THE MEDICAL JOURNAL OF AUSTRALIA

VOL. II.—36TH YEAR. SYDNEY, SATURDAY, SEPTEMBER 17, 1949. No. 12.

Table of Contents.

[The Whole of the Literary Matter in THE MEDICAL JOURNAL OF AUSTRALIA is Copyright.]

ORIGINAL ARTICLES— Page.
The Hyperventilation Syndrome, by W. Andrew Dibden, M.B., B.S., D.P.M. .. 409
Toxicity of Drugs Used in Local Anæsthesia, with the Report of a Fatal Case, by J. F. McCulloch, M.B., Ch.M., M.R.A.C.P. .. 416
A Case of the Schönlein-Henoch Syndrome, by J. Allsop and K. Viner Smith .. 418
The Use of Urethane in Leuchæmia, by Ian Collins 420
Otogenic Brain Abscess, by Volney Bulteau .. 423
Otogenic Abscess, by Gilbert Phillips .. 426
Some Observations on Biopsy Studies in Diseases of the Gall-Bladder and Obstructive Jaundice, by J. W. Perry .. 427

REPORTS OF CASES—
A Case of Alzheimer's Disease with Amyloidosis of the Vessels of the Cerebral Cortex, by S. Benedek and V. J. McGovern .. 429
A Case of Nutritional Disease of the Liver Treated with Choline and Studied by Serial Aspiration Biopsies of the Liver, by H. W. Garlick, M.R.A.C.P., and R. Motteram, M.B., B.S., B.Sc. 430
Two Unusual Abnormalities of Meckel's Diverticulum, by G. M. B. Hales .. 431

REVIEWS—
Papers on Psycho-Analysis .. 432

BOOKS RECEIVED .. 432

LEADING ARTICLES—
The Cytological Diagnosis of Malignant Disease .. 433

CURRENT COMMENT—
Nutritional Factors in Antibody Formation .. 434
Diphtheria in Greece .. 435
The Treatment of Scarlet Fever .. 435
Twitching of the Eyelids .. 436
Bronchoscopic Studies in Primary Tuberculosis .. 436
Spontaneous Remissions of Acute Leuchæmia .. 437
A Canadian Course in Aviation Medicine .. 437

ABSTRACTS FROM MEDICAL LITERATURE— Page.
Pathology .. 438
Morphology .. 439

BRITISH MEDICAL ASSOCIATION NEWS—
Scientific .. 440
New South Wales Branch News .. 441

CORRESPONDENCE—
Pregnancy and Intestinal Obstruction: A Dangerous Combination .. 442
B.C.G. Vaccination Against Tuberculosis .. 442

POST-GRADUATE WORK—
The Melbourne Permanent Post-Graduate Committee .. 442
The Post-Graduate Committee in Medicine in the University of Sydney .. 443

CONGRESSES—
An Ophthalmological Congress in America .. 443

NAVAL, MILITARY AND AIR FORCE—
Appointments .. 443

DISEASES NOTIFIABLE IN EACH STATE AND TERRITORY OF AUSTRALIA .. 443

AUSTRALIAN MEDICAL BOARD PROCEEDINGS—
Tasmania .. 444
Queensland .. 444

OBITUARY—
Brynmor Beveridge Jones .. 444

NOMINATIONS AND ELECTIONS .. 444

DIARY FOR THE MONTH .. 444

MEDICAL APPOINTMENTS: IMPORTANT NOTICE .. 444

EDITORIAL NOTICES .. 444

THE HYPERVENTILATION SYNDROME.[1]

By W. ANDREW DIBDEN, M.B., B.S. (Adelaide), D.P.M. (Melbourne),
Adelaide.

"SYNDROME" is defined as "the aggregate symptoms of a disease; a complex of symptoms" (Scott, 1926). The term "hyperventilation syndrome" is purely descriptive. The condition cannot be considered a disease entity; it is "a complex of symptoms" associated with overbreathing. Because, no doubt, of its dramatic nature, spontaneous hyperventilation tetany has received considerable attention in the literature (Fowweather, Davidson and Ellis, 1940; McCance and Watchorn, 1937; O'Donovan, 1942; Schultzer and Lebel, 1939; Wingfield, 1941). It is important to realize, however, as Kerr, Dalton and Gliebe (1937), Silberberg (1942), and others (Baker, 1934; O'Donovan, 1943; Anderson, 1941; Sargant, 1940; Maytum, 1938; Maytum and Willius, 1934; Stead and Warren, 1943; Gliebe and Auerback, 1944) have pointed out, that many clinical manifestations other than typical tetany may be the result of hyperventilation. Fowweather, Davidson and Ellis (1940), after discussing five cases of spontaneous hyperventilation tetany, conclude that the clinical manifestations arising from hyperpnœa cover a field much wider than that conveyed by the term "tetany"; they support the use of the much broader expression "hyperventilation syndrome". The importance of the syndrome lies in the fact that it is so frequently overlooked, and that patients showing it are often given a label of organic disease which inevitably tends to make their condition worse.

[1] Read at the annual meeting of the South Australian Branch of the Australasian Association of Psychiatrists on March 8, 1949.

Physiology.

The first observations on the signs and symptoms that result from voluntary overbreathing were made by Haldane and Poulton (1908). In their paper they record that, in Poulton, about one minute of hyperventilation produced tingling in the hands and sometimes to a slight extent in the feet. This became painful, the pain reaching a maximum usually about half a minute after the apnœa had begun. The tingling was accompanied by numbness and sweating of the hands and by a peculiar sense of giddiness and "abnormality" almost resembling the effects of anoxæmia. The same symptoms were noticed in J.R.K.M., but except for the feeling of "abnormality" were almost absent in J.S.H. even after five minutes of forced breathing. Best and Taylor (1945) describe fully the effects of forced breathing:

> Probably the first subjective observations of the student will be dizziness and faintness resulting in some relaxation of his efforts. . . . This initial discomfort may arise from a disturbance of the circulation directly due to the too vigorous movements of the chest, and for this reason instructions are given to assume the supine position and to force the depth rather than the rate of breathing. Within five minutes at the most, a regular rhythm has been established and the subject will have begun to notice numbness and tingling, probably coolness and perhaps tremors in various part of the body and slight tightening of the muscles. . . . The pulse and blood pressure will have risen, as would be expected with muscular exercise, but from now on signs and symptoms will begin to vary. The pulse and blood pressure may retain their relationship, or the pulse may arise without corresponding rise in pressure, but not infrequently the pulse rate increases while the pressure falls. It is usually in this last group of cases that one may find the cold clammy skin, pale cyanosis and thready pulse which form a curious anomaly. . . . Good evidence of circulatory disturbance exists in the

> coldness of the extremities. . . . Tetany varies from a slight stiffness of the muscles to well-marked contractures. In the hand the most common attitude is ulnar flexion with relative extension on the radial side and some flexion of the wrists.

It has been shown (Grant and Goldman, 1920; Collip and Backus, 1920) that the forced breathing washes out carbon dioxide and produces a state of alkalosis and an increase in the pH of the blood. The tetany of alkalosis, and its relationship to parathyreoid tetany, are not easy to explain upon the basis of calcium deficiency, since in this type the serum calcium level is not significantly lowered. It has been suggested, however (Best and Taylor, 1945), that the shift of the acid-base balance to the alkaline side causes a reduction in the ionic calcium without altering the total calcium concentration. Barnes and Greaves (1936) postulated that there was a fall in ionic calcium level in hyperventilation tetany. They assumed that the calcium level in the cerebro-spinal fluid was an index of the diffusible calcium of the blood; they based their postulate on the fact that they found "a definite drop" in the cerebro-spinal fluid calcium level. It is doubtful whether the assumption that the cerebro-spinal fluid is simply an ultrafiltrate is warranted; it is more probable that the cerebro-spinal fluid is actively secreted by the chorioid plexus (Best and Taylor, 1945). Further, the administration of parathyreoid extract or the injection of calcium salts, both of which raise the diffusible calcium level of the plasma, causes little rise in the calcium concentration of the cerebro-spinal fluid; it is little affected by parathyreoidectomy. McCance and Watchorn (1937) disagreed with the assumption made by Barnes and Greaves, and showed in a case of spontaneous overbreathing tetany that there was no change in the cerebro-spinal fluid calcium level. McLean and Hastings (1935) confirmed what Grant and Goldman had stated in 1920, that the tetany of alkalosis does not appear to be associated with a diminished concentration of calcium ions in the plasma. Others (Scott and Cantor, 1933; Schultzer and Lebel, 1939; Gunther and Greenberg, 1931) have shown that not only is there no fall in ionic calcium level, there may even be a rise; the calcium level of the cerebro-spinal fluid may show no change or even a slight rise. Talbott *et alii* (1938) have put forward evidence to support an hypothesis that the principal factor in producing hyperventilation tetany is diminution of pCO_2 and not increase of pH. The consensus of opinion is that the tetany is due to the alkalosis itself and not to any change in calcium ions.

Observations on forced breathing reveal the following points of importance. (*a*) The symptoms appear in order and increase in severity; they follow a gradient, the earliest symptoms being often hard to describe and most frequently related to a subjective change in consciousness or equilibrium. This explains why the hyperventilation syndrome is easily overlooked; the complaints are so vague and indefinite as to be dismissed as "imaginary". Then again the patient has probably been unaware of any quickening or disturbance of respiration. Hinshaw, Rushmer and Boothby (1943) point out that, though the results of extreme hyperventilation are well known, it has not been adequately emphasized that similar results are produced by hyperventilation continued over a longer period of time. Beckman (1945) observed that moderate hyperpnœa over a period of hours might cause severe cramp of voluntary muscles. (*b*) The reaction to hyperventilation varies greatly: the gradient of symptoms is individual to the subject. This was shown in Haldane and Poulton's original observations (1908) previously quoted. McCance and Watchorn (1937) also demonstrated that the ease with which tetany can be induced by overbreathing has little diagnostic significance. Perfectly normal people may be as susceptible to alkalosis and tetany as those unfortunate people who are liable to attacks of uncontrollable overbreathing and its alarming sequelæ. (*c*) Cases of "hypersensitivity" occur. O'Donovan (1942) reported details of a patient in whom tetany was readily induced by hyperventilation for nineteen to thirty seconds. The reason for this extreme sensitivity to alkalosis is not positively explained. It will be discussed later.

Causes of Hyperventilation.

Best and Taylor (1945) state that hyperpnœa may result from impulses reaching the respiratory centre from the cerebral cortex (as in excitement and other emotional states) or from the hypothalamus; by the stimulation of sensory nerves (for example, pain, heat or cold applied to the skin, *et cetera*); by conditions which increase the demand of the tissues for oxygen—for example, muscular exercise. Fowweather *et alii* (1940) write that there are numerous causes of overbreathing which may give rise to tetany.

> They include certain cerebral conditions which presumably operate by some effect on the respiratory centre, exercise, pain, and nausea. The great majority of cases, however, have little or no recognizable organic background, but occur in those suffering from anxiety states, hysteria, or psychoneuroses, and the patients are for the most part young women.

From my own observations, I have come to divide up the causes in the functional cases under three general headings, as follows.

Exertion.

The respiratory response to exercise varies tremendously from individual to individual, and has a definite relationship to what we call "fitness"—that state of endurance and capacity for work which results from training and practice. One has only to compare the average sedentary worker with the trained athlete when both are running for a motor bus to notice the relationship of breathlessness to effort. The nervous person tends to be an unfit person. Because of narcissistic preoccupations there is a general withdrawal from social contacts and physical activities. Selfconsciousness reduces recreational pursuits. Overanxiety causes undue emphasis to be placed upon symptoms, and a defensive attitude to be taken up directed towards the elimination of any activity imagined as likely to do harm. How often do we find nervous patients giving up more and more of their accustomed activities, on the assumption that the physiological changes experienced after excitement or exertion are detrimental? Exercise, therefore, in nervous individuals may have the apparently paradoxical effect of causing alkalosis: the exercise produces a physiological increase in pulmonary ventilation —which is, however, excessive to the amount of work done and which tends to be carried on unduly past the termination of the work, the result being a washing out of carbon dioxide and alkalosis. Herxheimer (1946) discusses this tendency to overbreathing as a result of exercise in his presentation of five cases of hyperventilation asthma. Lawrence and McCance (1930) studied a case of tetany after exercise. They clearly established the ætiology of the tetany, which proved to be alkalæmic and to follow functional overbreathing after the cessation of the exercise.

CASE I.—J.P.T., an ex-serviceman, aged thirty years, had first noticed nervous symptoms during active service in November, 1943. He came out of action with malaria, but stated that the exciting factor of his nervousness was being caught in bomb blast. He was admitted to a psychiatric hospital in March, 1944. He complained of headache, lack of concentration, "blackouts", insomnia, depression, fatigue, nausea. He was treated and discharged from the army at the end of 1944. He was admitted to hospital with a recrudescence of symptoms in February, 1947, in March, 1948, and again in August, 1948. Constitutionally, he had shown neurotic tendencies from childhood; his mother and two sisters were nervous, and he had had an actual "nervous breakdown" fourteen years earlier. On February 1, 1949, he stated that he had been involved in a minor motor-car accident two weeks previously and had had a relapse of symptoms. He said he had been working well and was disappointed that he had "packed up" again. He complained of a feeling of extreme weakness and of tremor of the hands on even slight exertion, so that he could neither work in his garden nor carry on his job, which involved considerable walking. If he rested, he felt fairly well; but the symptoms appeared as soon as he exerted himself. A hyperventilation test was carried out. Overbreathing for one and a half minutes reproduced the feeling of extreme weakness and a visible coarse tremor of the hands, the symptoms he described.

Emotion.

We sigh with sorrow, we pant with rage, and we become short of breath with fear. Cannon (1920) has shown that an increase in pulmonary ventilation takes place as one of the automatic bodily changes in pain, hunger, fear and rage. It is not surprising, then, that respiratory disturbances are frequent among nervous patients. Spirographic recordings of such respiratory disturbances have been made by Christie (1935) and by Finesinger (1943). My own belief is that hyperventilation occurs much more frequently than we have hitherto acknowledged. For ease and clarity of presentation of the facts to patients, it is convenient to divide emotional reactions into two large groups: those associated with the primitive physiological state of fear, and those associated with the closely related state of rage. The autonomic changes are the same and represent the reflex sympathetico-adrenal response of the animal in danger: the reaction of flight (fear) and fight (rage) (Cannon, 1920). Under "fear", we can group those patients in whom frank fear, anxiety, worry or guilt plays the predominant role. Under "rage" fall those cases in which aggressiveness, resentment, a sense of grudge or injustice, bitterness, frustration, and an inability to modify one's environment are causal. Though one or other predominates, there is most often a combination of both.

CASE II.—S.W.R.D., a married man, aged twenty-nine years, stated that he had had his first attack when he was aged fifteen years. It came on near the middle of the night, and he could describe it only as "a paroxysm of fear"—it did not seem to be "a normal sort of fear". He has had these attacks ever since. When the fear grips him he has a strong desire to go outside, to start walking, to run away from something, to do anything but remain still in bed. Of late years, these attacks have left him with a deep depression which he finds difficult to shake off. He has difficulty in concentrating. Asked to describe what happens in an attack, he stated that he wakes with a start and with the feeling of dread; he notices extreme giddiness, a sense of unreality and an urgent desire to move about; palpitation of the heart, tautness of muscles and clamminess are present. He stated that he had no fear of dying, but was afraid of going to bed as he dreaded the attacks. Later he admitted to a strong fear of becoming insane. As a child, he was inclined to be "shut-in" and to brood; he was self-conscious and did not make friends readily. A hyperventilation test was carried out. Flushing of the face was apparent after fifteen seconds, and the patient stopped the forced breathing, clasped his head in his hands and dropped his head between his knees. He said he felt giddy and was disinclined to carry on with the test. He admitted that it was the same feeling as he had in his attacks, through of less intensity.

Fear was revealed in his recollection that when he was about thirteen years old he was detected masturbating by his parents and was told that the practice could lead to insanity. He gave up the habit for a time, but then resumed it. But he admitted that he feared the consequences of his masturbating, and that when he had his first attack he interpreted it in the light of this warning. Ever since, the attacks have been associated with this dread of losing his reason. However, rage was revealed in another memory: that his mother was not well nervously and was irritable when he was aged about twelve to fifteen years. He felt that he bore the brunt of her wrath. One thing he resented very much was being smacked across the face. He recalled that, just prior to the first attack, his mother had smacked him across the face, and that he had left home and spent the day in a vacant allotment, not returning home for food until it was dark.

It is evident that rage was the emotion behind the first hyperventilation attack, but that the symptoms were subsequently interpreted in terms of his hidden guilt feelings, and fear thereafter became the motive force behind the attacks.

CASE III.—L.N.B., an ex-army chaplain, aged thirty-six years, complained that about four months earlier he had felt "all-in". Then, suddenly, he noticed dizziness, weakness, pain in the back of the head, palpitation, shortness of breath, coldness, trembling. He thought he was about to have a stroke. A doctor was called and could find no evidence of organic disease. He went for a holiday to the country, but had three similar turns there. He feared that he might go insane. In the past two weeks he had gained strength; but he still could not concentrate, and was easily upset, anxious and irritable; he had mild dizzy spells, headaches and palpitation, and noticed a feeling of constriction about the chest. A hyperventilation test was carried out. The patient overbreathed for one and a half minutes. He noticed dizziness in half a minute, and then all the abovementioned symptoms appeared, though in less degree than in his attacks. He readily admitted that the feelings were the same as those complained of.

The patient had been a prisoner of the Japanese for three and a half years, and had suffered from debility and beriberi. After his discharge from the army early in 1946, he studied for an arts degree for two years, holding at the same time the post of chaplain at a university college. In January, 1948, he was appointed a master and assistant chaplain at a large boys' college. Soon after his appointment the chaplain died suddenly, and the full responsibility fell upon him. He then had almost a double job: he taught lessons five days a week and gave two short religious services daily; and at the week-end he officiated at weddings, baptisms and three full services on Sunday. As well, he noticed a symptom not uncommon among ex-prisoners of war—that of intense fatigue coming on in the early afternoon. Just before his first attack he had begun to feel the strain and to become very tired. He was of a conscientious, anxious disposition. A brother was at the same time suffering from a manic illness.

The main emotions in this case would appear to be: resentment at the apparent lack of sympathy of the principal of the school, in that the patient was expected to carry on doing double duties; frustration in having to try to cope with more than he could manage; fluster in attempting to keep up with the work. Of course, later, anxiety at the possible significance of the attacks was added to the picture.

These two cases illustrate the relation of emotions to the hyperventilation syndrome. My own belief (though unsupported by statistical evidence) is that the aggressive impulses are more frequently productive of the syndrome than fear states.

Heat.

Heat is lost from the body in the breath, and an increase in respiratory volume is one way of cooling the organism. This mechanism is seen at its best in the panting of dogs (Anrep and Hammouda, 1932). In hot, humid weather, when heat loss by the evaporation of perspiration and direct radiation is reduced, there is a tendency to overbreathe. Landis *et alii* (1926) produced hyperpnœa, with a pH change of the blood to the alkaline side and definite tetany, in human subjects by immersion in a hot bath, the temperature of which was gradually raised. Earlier, Bazett and Haldane (1921) had observed the effects of hot baths on man. They record that J. B. S. Haldane, when immersed in a bath with a temperature of 37·2° C. rising at 0·13 degree per minute, breathed 27·3 litres per minute against a normal of 6·0 litres per minute. During this hyperpnœa, the alveolar carbon dioxide fell from 38·7 to 25·6 millimetres partial pressure. The hyperventilation was accompanied by faintness, mental confusion and tingling which were relieved by the breathing of mixtures containing 8·5% carbon dioxide and 14·2% oxygen or equal volumes of air and carbon dioxide. Wingfield (1941) recorded a case of hyperventilation tetany which occurred spontaneously in the Persian Gulf, and which was considered to be due to the heat. The following case is of interest.

CASE IV.—N.H.W., a plumber, aged thirty-one years, consulted me in March, 1946. He complained that since August, 1945, though rarely before, he had had "blackouts": his vision "blacked out", he could see nothing. He recovered in a quarter to half a minute. Then he began to have dizzy feelings and to lose balance and to stagger when he walked. He became afraid to work for fear of climbing ladders and perhaps falling. Since December, 1945, he had noticed other turns: his face, mouth and tongue went stiff (he wanted to speak but could not); his hands and fingers went stiff and drew up across his body; there was a lack of sensation at first, but when relaxation occurred he noticed "pins and needles"; similar sensations occurred in the legs, starting in the thighs and working down to the knees; sometimes his toes curled up like the fingers. At the onset he noticed first a feeling of "internal pressure" from his forearm to his fingers, then his breathing became irregular and gasping. He did not lose consciousness, but, though aware of what was going on about him, he was unable to do anything. He admitted that he frequently had the feeling that he could not draw a decent breath. The "turns" occurred, as did the "blackouts", only

in hot weather. In cold weather he was "full of pep". He had one severe turn (probably an attack of hyperventilation tetany) while under a hot shower.

The patient was very tall (six feet six inches), thin and asthenic. He was highly strung, over-conscientious, meticulous, readily irritated by trifles. He was in some conflict about his work: he did not like it particularly, but had to stay at it as it was his father's business and he would one day inherit it. A hyperventilation test was carried out. The patient would not breathe very deeply, and overbreathing was continued for three minutes. This produced tightness and numbness in his face and numbness and "pins and needles" in his fingers and toes. He admitted that it was just like the early part of an attack.

In this case the diagnosis was aided by the fact that the attacks occurred only in hot weather, and that one started while the patient was under a hot shower.

Comment.

The three causes discussed may occur independently, but more usually two or even the whole three causes combine to induce attacks.

I have mentioned that nervous people tend to be unfit people. Then again, nervous people often undertake exertion in some trepidation, fearing that they may do themselves some harm or dreading that they may faint or collapse and so humiliate themselves in the eyes of onlookers. Many of them declare that they feel worse in hot weather. It is interesting to note that Soley and Shock (1938) subscribed to the belief that exertion *plus* anxiety led to hyperventilation and that the latter, by producing respiratory alkalosis, was responsible for the symptoms of effort syndrome.

Ætiology.

The hyperventilation syndrome is, in most cases, an expression of a personality inadequacy. My impression is that it occurs most often in patients with anxiety hysteria, in obsessive, aggressive personalities. The attack itself may be precipitated by quite trivial stresses, just the pinpricks and frustrations of everyday life. I have mentioned already my belief that the emotions allied to primitive rage are more productive of the syndrome than those of fear. Silberberg (1942) holds that sighing dyspnœa is more common in females than in males. Fowweather *et alii* (1940) state that patients are for the most part young women; admittedly they were referring to cases of hyperventilation tetany. Though I cannot as yet give statistics, I think that the lesser degrees of respiratory alkalosis occur quite as frequently in men as in women.

Symptoms.

Guttmann and Maxwell Jones (1940) state that the symptoms produced in a normal man by overbreathing fall into sets: (i) a tetanic type, and (ii) some disturbance of consciousness. Tingling in the finger tips (or in the toes or lips), numbness of the extremities, stiffness, and a tendency to characteristic postures (*main d'accoucheur*) up to fully developed tetanic spasms, belong to the former group; the description of the symptoms of the latter group varies, not only with their intensity, but also with the subject's capacity for self-observation and expression. Numbness in the head, dizziness, a far-away feeling, a faint feeling, a sleepy feeling, and fatigue, seem to be synonymous for describing the same feeling; and the "giddiness" often mentioned apparently does not signify rotatory vertigo but the same impairment of consciousness. Haldane and Poulton (1908) refer to the peculiar sense of giddiness and "abnormality". Silberberg (1942) and Sargant (1940) also draw attention to the fact that many such symptoms usually occur before, often in the complete absence of, the carpopedal spasms of tetany.

It is essential to be familiar with these vague early symptoms if the occurrence of hyperventilation in neurosis is not to be missed. Whenever a patient makes the statement "I have turns when I feel as if I am going to faint", and in the absence of organic disease, I have a hyperventilation test performed. Other symptoms I find suggestive of the syndrome are as follows: giddiness, a sense of unreality, a sensation of impending collapse; attacks of fairly generalized tremor, and feelings of weakness and exhaustion ("I feel as if all my strength has drained out of me"). A number of patients complain of a feeling of constriction across the chest. Wood (1941) has drawn attention to this paradoxical effect: the hyperventilation, because of this feeling of constriction, produces a desire to take a deep breath, and the response to this desire prolongs the hyperventilation. At times the emphasis is on some less prominent manifestation, and it is easy to miss the mechanism—for example, Case I.

It is important to realize that these symptoms are most unpleasant and frightening to the patient. In their more complete form they are also alarming to relatives and onlookers. Haldane and Poulton (1908) record the alarm induced in members of the Physiological Society when their overbreathing experiment was first shown at a meeting of that august body in June, 1908:

> When forced breathing is continued for a longer period the apnœa lasts much longer, and the oxygen percentage in the alveolar air falls to such an extent that for a considerable time before the cessation of the apnœa the subject is blue in the face and presents a most alarming appearance, although he feels no desire to breathe. When this experiment was shown for the first time at a meeting of the Physiological Society some of those present thought that something was wrong with the subject of them (E.P.P.), and could hardly be hindered from performing artificial respiration. One or two were so much affected that they became faint or sick, and had to retire hastily. The face gradually assumes the leaden, corpse-like appearance characteristic of great anoxhæmia, and it may be about a minute after this change begins before any desire to breathe is experienced.

The Importance of the Hyperventilation Syndrome.

Hyperventilation is not the cause of the disorder; it is only a mechanism by which symptoms are produced. If psychoanalysis could be employed in the treatment of such cases, the syndrome would lose much of its significance. As the conflicts, repressions, and sources of anxiety and of tension were resolved, the tendency to overbreathe would also disappear. In practice, however, the majority of patients have to be treated by the shorter, more superficial methods of psychotherapy. It is probable that, even without the recognition of the syndrome, patients will respond and be relieved by reassurance, suggestion and encouragement. Nevertheless, the early recognition of this symptom complex materially shortens the duration of treatment. The reason for this is twofold:

1. The early symptoms of hyperventilation, especially those related to an alteration of the state of consciousness, act themselves as a source of anxiety. A conditioned reflex is set up. Just as it can be shown that harmless noises acted as conditioned stimuli to a fear reaction in nervous soldiers, so can the early symptoms of alkalosis themselves act as the trigger releasing an intense anxiety reaction which of course in turn tends to aggravate the hyperpnœa. A vicious circle is established, which is self-generating, and which can continue long after the original traumatic experience has lost its significance.

CASE V.—P.M.T., a married woman, aged twenty-seven years, was referred by an ear, nose and throat specialist because she complained of various symptoms around the throat for which he could find no pathological basis. He mentioned that she was afraid of a tuberculous laryngitis, from which her brother had died, but that there was no evidence of this condition.

The patient was extremely anxious and apprehensive when interviewed. She said that she had developed pulmonary tuberculosis some three and a half years earlier during her second pregnancy. With rest her condition had improved greatly, and the child was born uneventfully. Some twelve months prior to examination, only two weeks after her brother had died from advanced pulmonary tuberculosis and a tuberculous larynx, she discovered that she was again pregnant. This discovery threw her into a panic, as she felt sure she could not live through another confinement. However, she was reassured by her medical advisers and the pregnancy was again normal. The baby is now eight months old. Six months prior to examination she noticed some cough and sputum, but paid little attention

to these symptoms. Four months prior to examination she began to lose weight and to be always tired and irritable, and her cough and sputum became worse. She was reexamined. Her doctor advised her over the telephone that the test of her sputum had given a positive result. When the doctor confirmed her query that this meant that the disease was "active", she said she "couldn't talk". The feelings in her throat had been present since that night.

The first thing the patient noticed was a "funny feeling" of hot and cold generally. Then she felt a tightness ("just like a hand gripping") in her throat. Sometimes she had a "feathery feeling" in the top part of her chest and a sense of constriction. She was conscious of her heart thumping. Later her arms and legs shook, and she felt weak in the legs and exhausted. She had the most acute feeling of fear and was afraid to be alone. She had always been highly strung, and was full of fears as a child. When she was aged seven years, she was away from school for a year on medical advice; she said that she "couldn't bear to be away from her mother".

A hyperventilation test was carried out. A frightened look appeared on the patient's face after half a minute, and she would not continue the overbreathing past one minute. She became panicky and taut; her hands were clenched and her face drawn; she cried fearfully and looked on the verge of collapse; she clutched at her throat and showed a distinct tendency to go on heaving for breath. She calmed down with reassurance, but began to tremble noticeably and to complain of weakness. She admitted that the sensations brought on were identical with her "turns", and that the feeling of constriction in the throat was the same.

"Fear gripped her in the throat" when she first heard of the reactivation of her pulmonary disease. This anxiety symptom was misinterpreted in terms of her brother's terminal condition and increased her dread. Other factors tended to perpetuate the anxiety reaction: her husband was away from home a large part of the time (he was an airways pilot), and she dreaded being alone for fear of what might happen in her "turns", and resented being left to bear the responsibility of looking after her home and children alone and in her present state of health. The reassurances of doctors were unavailing because her symptoms still appeared.

In practice, I have encountered the following fears engendered by the symptoms of hyperventilation: of fainting or collapse; of dying; of having or being about to have a stroke; of heart failure; of insanity. Secondary fears quickly accumulate: of being left alone in case something dreadful happens and no one will be about to render aid; of excitement or emotional upset of any sort; of crowds or the city streets; of impending disaster, and so on.

2. The reproduction of the symptoms complained of, at will, by the simple hyperventilation test is a most dramatic, convincing, and yet reassuring, experience for the patient. The therapist is able then in simple terms to explain the physiological mechanisms involved and to point out their occurrence in normal people if hyperventilation is continued long enough. The patient is reminded how rapidly recovery took place after the test, and shown how he can abort or cure an attack by relaxation and the control of his breathing. Anxiety and a flight into panic are unwarranted and must aggravate the condition.

In many cases this reassurance is all that is required. Other patients need further sessions with reinforcement of the explanations, reassurance and encouragement. Still others require a deeper investigation of factors likely to be causing the original conflict between the personality and the environment, which may still be operating.

The Hyperventilation Test.

There is no great uniformity in the literature as to the method by which the various investigators have elicited symptoms by forced breathing. In their studies on effort syndrome, Guttmann and Maxwell Jones (1940) had their patients overbreathe for ten minutes or until the patient refused to continue owing to the symptoms produced; the number of respirations per minute is not given. Soley and Shock (1938) used a rate of 25 to 30 respirations per minute and apparently kept it going until symptoms were produced. Kerr, Dalton and Gliebe (1937) performed the test with the patient recumbent, at 18 to 20 respirations per minute for up to thirty minutes. Opit (1943) considers thirty minutes far too long, and suggests that, if symptoms have not been induced in five to fifteen minutes, the test should not be continued. O'Donovan (1943) had his patients take 55 to 60 breaths per minute, and classified those who developed tetany in less than two minutes, or who experienced such severe subjective symptoms within two minutes as to prevent their continuing the test, as a hypersensitive group; those who developed tetany in two to three minutes were in the borderline group.

This hypersensitivity to overbreathing is interesting. O'Donovan (1942) had a patient in whom tetany was induced by hyperventilation for nineteen to thirty seconds. Opit (1943) records that his patient noticed "pins and needles" in the hands within fifteen seconds, and spasmodic contractions of the fingers within three-quarters of a minute; "seizures" (generalized convulsive movements) and almost loss of consciousness occurred within two minutes.

The reason for this hypersensitivity is not clear. The work of McCance and Watchorn (1937) suggests there may be a constitutional factor, a variable susceptibility of the subject to alkalosis. On the other hand, Guttmann and Maxwell Jones (1940)) postulated that in some cases there is an habitual state of hyperventilation; and Schultzer and Lebel (1939) suggested that the "oversensitive" patient in their series was constantly in a state of latent tetany and thus required little further excitation to precipitate a frank attack. In research I carried out[1] on a group of nervous subjects and controls, the alveolar carbon dioxide level was measured as soon as the volunteer entered the experimental room; that is, the experimental situation was used as the stimulus of an emotional reaction. It was found that the carbon dioxide level of the group of nervous people as a whole was lower to a statistically significant degree than that of the control group. This suggests that in nervous people there is a tendency to a sighing type, or to a generally increased rate, of respiration; in other words, that they are always in a state of mildly reduced carbon dioxide tension.

I usually have the patient perform the test sitting up, for I believe the alterations to consciousness, the subjective sensations of giddiness and unsteadiness, are more quickly and easily induced in this position (contrast Best and Taylor's description quoted in the second paragraph of this paper). The rate of hyperventilation is roughly gauged at 30 breaths per minute, and the forced breathing is continued for two, sometimes three, minutes, unless the patient stops of his own accord before then. Often early symptoms occur within fifteen to thirty seconds of commencement of the test and can be detected by the observer in a change of expression, and sometimes of colour (flushing or pallor), in the patient's face. At the completion of the period of overbreathing, the patient is allowed to recover and is then asked to describe what he has noticed. The feelings experienced are compared with the symptoms complained of. Subjective alterations in consciousness and equilibrium are first to appear. It is interesting to note that coarse tremor and a sense of extreme weakness and exhaustion become most apparent during the recovery phase.

Diagnosis.

Organic disease must be excluded. For example, Barker and Sprunt (1922) report an instance of tetany during a paroxysm of hyperpnœa in a psychoneurotic patient convalescent from epidemic encephalitis. The syndrome may be suspected from the patient's history and description of the clinical symptoms, and is confirmed by the hyperventilation test.

Treatment.

The treatment of the condition can be divided into (*a*) treatment of the acute attack, and (*b*) treatment of the patient as a whole.

(*a*) The hyperventilation syndrome can be relieved by any measure which raises the alveolar carbon dioxide

[1] Work carried out in the Department of Physiology at the University of Adelaide with the aid of a part-time grant from the National Health and Medical Research Council.

pressure or which lowers the pH of the blood. Acute severe attacks can be cured by breathing "Carbogen", or by rebreathing into a paper bag. Less severe attacks are terminated by reassuring the patient, having him relax and breathe quietly and shallowly, or encouraging him to hold his breath for ten to fifteen seconds every minute or so. J. B. S. Haldane (1921) showed experimentally that the ingestion of ammonium chloride by man causes severe and prolonged acidosis. It would thus seem feasible to treat the syndrome with this drug. I did use it in the early stages of my interest in the syndrome, but I am unable to give any definite opinion as to its efficacy. It is unpleasant to take in mixture form. Nevertheless, several patients said they felt better for it. A number of authors have used calcium salts both in the treatment of attacks of tetany and in the more prolonged therapy of the hyperventilation syndrome. Fraser and Sargant (1938) advise intravenous injections of 10 cubic centimetres of a 5% solution of calcium chloride to stop hyperventilation tetany, and O'Donovan (1942) used three to 10 cubic centimetres of calcium gluconate solution intravenously for the same purpose. The last-mentioned author stated, too, that he cured his patient (already mentioned, who developed tetany after nineteen to thirty seconds' overbreathing) by continually raising the serum calcium level to the upper limits of normal by the administration of 400 to 800 milligrammes of calcium with vitamin *D* daily for two years. O'Donovan held that suggestion could play no part in the results. I use calcium and vitamin *D* ("Calvita" tablets, containing 500 milligrammes of tricalcium phosphate, 10 milligrammes of ferrous sulphate, one milligramme of vitamin B_1 and 500 international units of vitamin *D*—one to two tablets three times a day) as the only pharmacological approach to the problem of treatment, and rely on the conviction of the hyperventilation test, explanation and reassurance. Patients appear to be benefited by this combination, but it is always hard, if not impossible, to assess the efficacy of any drug when used in conjunction with psychotherapy. Nevertheless, my impression is that calcium and vitamin *D* are worth giving.

The mode of action of calcium is not decided, because the mechanism underlying the production of the symptoms of the hyperventilation syndrome has not been positively determined. It was pointed out earlier that the consensus of opinion is that the symptoms arise as a result of the raised pH of the blood, of the alkalosis itself, and not from any supposed alteration in the level of ionized calcium in the serum. The clinically observed fact that intravenous injections of calcium terminate attacks of hyperventilation tetany would appear to contradict this hypothesis. A possible explanation of the mode of action of calcium and a solution of the apparent contradiction are to be found in the observations of Hollo and Weiss (1924) and Fürst (1925), quoted by Kuntz (1945), that the acid-base balance of the blood can be changed in the direction of acidity by the administration of calcium.

(*b*) As has been emphasized before, the hyperventilation syndrome represents, not a disease entity, but a mechanism for the production of symptoms. Hence cure of the syndrome by drugs, explanation and reassurance is only part of the total therapeutic problem. It is undoubtedly an important part, for it lowers the state of central emotional tension by eliminating the vicious circle mechanism, and by easing discomfort it gives the patient confidence and encourages him to make a direct assault on any other psychological and environmental difficulties. Nevertheless, further attention may have to be paid to any environmental stresses or to any underlying personality disorder. Here, however, the patient differs in no way from many psychoneurotic, and the extent of this psychotherapy will depend upon the nature and severity of the conditions found to be present.

Other Applications of Hyperventilation.

Relation to Cardiovascular Disease.

Breathlessness is a common manifestation of cardiovascular disease. The relation of functional dyspnœa and hyperpnœa to effort syndrome has been discussed by numerous authors (Sargant, 1940; Soley and Shock, 1938; Guttmann and Jones, 1940; Wood, 1941; Spillane, 1940; Adams and Sturgis, 1919; White and Hahn, 1929; Drury, 1920; Jones and Scarisbrick, 1941). Soley and Shock (1938) concluded that the respiratory alkalosis resulting from hyperventilation produced the symptoms of effort syndrome. Wood (1941), in an admirable review, came to the conclusion that the total evidence indicates that hyperventilation cannot be held responsible for the symptoms and signs of da Costa's syndrome, neither by causing tissue alkalosis nor by interfering with the circulation, but that it does occur in some cases and when present must aggravate certain of the symptoms.

An important contribution has been made by Thompson (1943). He showed, by illustrative cases, that patients with the hyperventilation syndrome may have severe precordial pain with radiation to the arms, often suggesting the possibility of coronary artery occlusion. He also demonstrated that these patients frequently exhibit pronounced electrocardiograph abnormalities, consisting either of late inversion of the *T* wave, or of depression of the *S-T* segment with marked lowering of the *T* wave. Any or all leads may be involved. Changes in the *QRS* complex have been observed in but a single case, and were limited to lead 4F. These abnormalities disappear when recovery from the syndrome takes place, but may be reproduced by voluntary hyperventilation if recovery has not become too firmly established. Thompson emphasizes that, since severe precordial pain may be included in the syndrome, recognition of these pronounced electrocardiographic abnormalities assumes importance lest they be attributed to infarction of the heart, with the result that the anxiety state becomes worse. The following case of my own, I believe, exemplifies this point.

CASE VI.—A.G.B.J., a married man, aged forty-four years, while a member of the Royal Australian Air Force, on July 29, 1945, complained that that afternoon he had begun to feel "off colour" and had become conscious that his heart was thumping at a rapid rate. He thought he was going to die. He was "all of a tremble". The attack persisted for roughly two hours and he became short of breath. Examination revealed no abnormality. On August 13, 1945, he reported that he had been walking around the hangar when he felt suddenly giddy and noticed that his heart was beating rapidly. He was short of breath. Examination showed his pulse rate to be 130 per minute; this was the only abnormal finding, and the rate slowed with rest to 90 per minute. An electrocardiogram was taken on December 8, 1945. The report was as follows: "Rate 100. Regular sinus rhythm. General voltage low. R4 = T4. ST 1, 2, 3 slightly coned with high take off. T2 isoelectric to negative; T3 negative." It was stated that the tracing was compatible with myocardial fibrosis in an old posterior infarct. Clinically no abnormality was detected, but the diagnosis of "old coronary occlusion from which he has made a good recovery" was made. On February 15, 1946, he was still complaining of dizziness, "fluttering" in the ears, shortness of breath, and loss of energy. He stated that he was unable to sleep at night because he could not "get his breath" properly lying down, and often woke up with a jump. Examination revealed the patient to be a nervous, trembling man, obviously worried about himself, but with no evidence of organic disease. An electrocardiogram was taken on February 18, 1946. The report read as follows: "Rate 95; normal sinus rhythm. Normal conductivity. S-T interval iso-electric. Poor T waves in 2 and 3." The tracing was considered to be normal. His symptoms apparently continued unabated, for on June 9, 1947, it was recorded that his attacks had altered little since the first attack in 1944. He complained of frequent attacks of precordial pain and some associated dyspnœa. He had the feeling that he was going to die. He felt faint; rapid palpitations were present in his chest, and the pain started over the precordium and travelled down the left side of his abdomen. On some occasions the pain had gone down his left arm and his fingers had gone numb. In the attacks he was shaky; in fact, his "nerves" were "bad at any time". He felt as though something was pressing down on his head all the time. An X-ray examination revealed no cardiac enlargement. The electrocardiographic findings were considered to be within normal limits: "Rate 75; regular sinus rhythm. Amplitude slightly below average. T3 negative (? postural)." He was considered to have a cardiac neurosis.

When I examined the patient on February 22, 1949, it was apparent that he dreaded heart disease, for two reasons: (*a*) because his father and brother had died suddenly from heart attacks (his brother at the age of forty-six years),

and his sister had died from chronic heart disease; (*b*) because he interpreted the giddy tremulous attacks with palpitation at night as indicative of heart failure. He admitted that the fear of heart disease was always with him, and that he dreaded going to sleep because of the anticipation of further attacks. A hyperventilation test was carried out. Overbreathing for two minutes reproduced his symptoms in minor degree. He readily agreed that they were the same sensations, in a milder form, as those occurring in his attacks.

I believe that the electrocardiographic findings upon which the original diagnosis of "old coronary occlusion" was made were of the kind described by Thompson, and that from the outset this man has been suffering from the hyperventilation syndrome. There is no doubt that the diagnosis of coronary disease tremendously increased his anxiety and that it has done much to fix the neurosis.

Relation to Aviation Medicine.

Uihlein and Boothby (1942) draw attention to the fact that symptoms of hyperventilation—namely, dizziness, faintness, tingling sensations, and involuntary muscular spasms especially of the hands and feet—may be induced by air-sickness and fear (sometimes subconscious fear), and may be associated with or aggravated by a state of emotional tension. The importance of recognizing the signs and symptoms of hyperventilation among flying service personnel, as well as among passengers, is obvious. Hinshaw, Rushmer and Boothby (1943) consider the same problem and point out that, though hyperventilation symptoms are usually seen among people of unstable nervous temperament, it is probable that persons who have normal emotional control may under unusual conditions become frightened or anxious sufficiently to suffer similar respiratory disturbances with the production of identical symptoms. Such stresses should occur in the field of aviation and particularly in combat flying more often than in any other field of human endeavour. The symptoms are of such a nature as to interfere seriously with a pilot's ability to control an aeroplane should they occur during flight. The following is a case of the hyperventilation syndrome occurring in an air hostess, whose previous history was clear and whose personality would appear to have been stable.

CASE VII.—M.B., aged twenty-three years, had been an air hostess for the past ten months. Three weeks prior to the consultation, whilst on a flight from Adelaide to Melbourne, she had felt "all funny" and vomited. On her next two flights, from Adelaide to Darwin, she had again vomited. On the day before she consulted me, she felt "nervous and on edge" as she was about to board the plane for the return flight from Darwin. On the way down, she again began to "feel funny", as if she could not get her breath, and her hands became stiff and she vomited. She had "pins and needles" in her fingers and toes, and felt as if she was going to faint. She was very worried over herself: "I have never been sick; its so silly to be like this." A hyperventilation test was carried out. Overbreathing for two minutes reproduced all her symptoms, except the vomiting. The latter was considered to be ordinary air-sickness in a person in a tense state.

The following emotional factors seemed to underly the hyperventilation syndrome. Her fiancé was a final year medical student and they had planned to marry immediately he had obtained his degree. However, he had failed in his final examination three months before her illness, and the wedding had had to be postponed. Five weeks before her illness, after living in a flat in Melbourne for some eight months, she had returned home. Here she came into mild conflict with her mother. The latter gave her "kindly advice": considered that she kept too late hours and did not have enough rest. Both the patient and her fiancé appeared to resent this as an intrusion on their rights as adults.

Relation to Epilepsy.

The ability to induce, by hyperventilation, seizures in some epileptics is well known. Hyperventilation is used as a routine measure in electroencephalography to bring out dysrhythmias, if they exist. Brill and Siedemann (1942, 1941) consider that the dysrhythmia may indicate a regression to a more primitive type of cortical activity, and that this activity appears when the normal physiology of the brain is disturbed by the fluctuations in blood chemistry brought about by hyperventilation. In other words, the most recently acquired functions are lost first, as a result of the alkalosis, the more primitive activity being "let go"—an expression of Hughlings Jackson's law (1884). The inverse is true. Koenig and Groat (1945) demonstrated experimentally that the excitability of the nervous system was depressed as a result of acidosis. They drew attention to the use of ammonium chloride, a ketogenic diet and other acidifiers in the treatment of epilepsy.

The hyperventilation syndrome should always be considered in the differential diagnosis of a suspected (especially if atypical) case of epilepsy. If the patient is witnessed at the end of a period of spontaneous hyperventilation, the heavy breathing followed by apnœa, the muscular spasms and contractures of tetany, especially if accompanied by a coarse marked tremor, may suggest an epileptiform seizure. Frazer and Sargant (1938) describe such attacks of tetany, which may simulate epilepsy. These authors state that in the more severe forms of hyperventilation tetany there may be actual loss of consciousness. Frequently it will be found, on close questioning of the patient, that consciousness has not actually been lost, only interfered with to the extent that a "far-away", helpless feeling is produced. One patient already mentioned (Case IV) described such an attack. He said he vaguely knew what was going on about him, but could neither speak nor indicate in any way that he was aware. To the observer, then, he could appear "unconscious". In view of the prevalent use by patients of the word "blackout" nowadays, it is important to make certain whether a patient has suffered a complete loss of consciousness or not. The diagnosis can be made by a careful history and description of the attack, if the possibility of hyperventilation tetany is kept in mind. Confirmation can be obtained readily by means of a hyperventilation test. If his condition is misdiagnosed, such a patient may be subjected to a long and unnecessary series of investigations, lumbar puncture, air encephalography, even ventriculography.

Discussion and Conclusions.

In this paper, emphasis has been placed on the importance of the hyperventilation syndrome in the production of a group of symptoms which, in many cases, the patient finds difficult to describe, and which can thus readily be brushed aside as "neurotic" or "imaginary". Or, conversely, the symptoms may be mistaken as indicative of some organic disease, such as epilepsy or cardio-vascular disease, and treated as such, with unfortunate results for the patient. Attention has been directed to the unpleasant and frightening nature of the symptoms, not only to the patient, but also to relatives and onlookers.

The impression is held that hyperventilation is considered by doctors all too frequently only in relation to tetany. We must be familiar with those other symptoms that present in the total absence of tetany and are so often overlooked.

It has been stressed that the hyperventilation syndrome is not a disease, but the mechanism of production of a complex of symptoms. Its recognition is important, however, for the complete understanding of the dynamics of the case, and because conditioned anxiety responses may be set up to the symptoms of hyperventilation and tend reflexly to perpetuate the condition. Its recognition, too, greatly shortens the duration of treatment, because the dramatic demonstration of the nature of the symptoms by the hyperventilation test so impresses the patient as to create an excellent *rapport* with the psychiatrist for further effective psychotherapy, besides convincing the patient of the functional nature of the symptoms and so lessening his anxiety. Nevertheless, the demonstration of the hyperventilation syndrome and its removal by psychological and pharmacological means are frequently not enough. The syndrome mostly occurs on a basis of emotional disturbance or psychoneurosis. The underlying emotional, environmental and personality factors must be dealt with if the patient is to benefit in any lasting fashion.

An underlying purpose of the paper, which has governed the selection of the material presented, has been to draw attention to the physiological and biochemical fact that, in the respiratory system of gaseous exchange, there lies

a sensitive mechanism by which rapid variations in the homœostasis of the organism can be brought about. Through the close bond between the emotions and the respiratory rhythm, there exists a means by which mental processes can effect profound and distressing physical changes. It is believed that the facts may have far-reaching implications.

References.

Adams, F. D., and Sturgis, C. C. (1919), "Note on the Vital Capacity of the Lungs and the CO_2 Combining Capacity of the Blood in Cases of Effort Syndrome", *The American Journal of the Medical Sciences*, Volume CLVIII, page 816.

Anderson, G. H. (1941), "Hyperventilation Syndrome", *Northwest Medicine*, Volume XL, page 243.

Anrep, G. V., and Hammouda, M. (1932), "Observations on Panting", *The Journal of Physiology*, Volume LXXVII, page 16.

Baker, D. M. (1934), "Sighing Respiration as a Symptom", *The Lancet*, Volume I, page 174.

Barker, L. F., and Sprunt, T. P. (1922), "A Spontaneous Attack of Tetany During a Paroxysm of Hyperpnœa in a Psychoneurotic Patient Convalescent from Epidemic Encephalitis", *Endocrinology*, Volume VI, page 1.

Barnes, C. G., and Greaves, R. I. N. (1936), "The Role of Calcium in Spontaneous Overbreathing Tetany", *The Quarterly Journal of Medicine*, New Series, Volume V, page 341.

Bazett, H. C., and Haldane, J. B. S. (1921), "Some Effects of Hot Baths on Man", *The Journal of Physiology*, Volume LV, page 4.

Beckman, W. G. (1945), "A Further Study on Muscular Cramps and the Hyperventilation Syndrome in Flyers in E.T.O.", *The Journal of Aviation Medicine*, Volume XVI, page 101.

Best, C. H., and Taylor, N. B. (1945), "The Physiological Basis of Medical Practice", Fourth Edition.

Brill, N. Q., and Seidemann, H. (1942), "Electroencephalographic Changes During Hyperventilation in Epileptic and Non-epileptic Disorders", *Annals of Internal Medicine*, Volume XVI, page 451; (1941), "The Electroencephalogram of Normal Children", *The American Journal of Psychiatry*, Volume XCVIII, page 250.

Cannon, W. B. (1920), "Bodily Changes in Pain, Hunger, Fear and Rage".

Christie, R. V. (1935), "Some Types of Respiration in the Neuroses", *The Quarterly Journal of Medicine*, New Series, Volume IV, page 427.

Collip, J. B., and Backus, P. L. (1920), "The Effect of Prolonged Hyperpnœa on the CO_2 Combining Power of the Plasma, the CO_2 Tension of Alveolar Air and the Excretion of Acid and Basic Phosphate and Ammonia by the Kidney", *The American Journal of Physiology*, Volume LI, page 568.

Drury, A. N. (1920), "The Percentage of CO_2 in the Alveolar Air, and the Tolerance to Accumulating CO_2 in Cases of So-called 'Irritable Heart' of Soldiers", *Heart*, Volume VII, page 165.

Finesinger, J. E. (1943), "The Spirogram in Certain Psychiatric Disorders", *The American Journal of Psychiatry*, Volume C, page 159.

Fowweather, F. S., Davidson, C. L., and Ellis, L. (1940), "Spontaneous Hyperventilation Tetany", *British Medical Journal*, Volume II, page 373.

Fraser, R., and Sargant, W. (1938), "Hyperventilation Attacks: A Manifestation in Hysteria", *British Medical Journal*, Volume I, page 378.

Fürst, K. (1925), *"Verminderung der Entzündungsbereitschaft durch Säurezufuhr"*, *Archiv für experimentelle Pathologie und Pharmakologie*, Volume CV, page 238.

Gliebe, P. A., and Auerback, A. (1944), "Sighing and Other Forms of Hyperventilation Simulating Organic Disease", *The Journal of Nervous and Mental Disease*, Volume XCIX, page 600.

"Gould's Medical Dictionary", 1926, edited by Scott, R. J. E.

Grant, S. B., and Goldman, A. (1920), "A Study of Forced Respiration Experimental Production of Tetany", *The American Journal of Physiology*, Volume LII, page 209.

Gunther, L., and Greenberg, D. M. (1931), "The Diffusible Calcium of the Blood Stream in Tetany", *Archives of Internal Medicine*, Volume XLVII, page 660.

Guttmann, E., and Jones, Maxwell (1940), "Hyperventilation and the Effort Syndrome", *British Medical Journal*, Volume II, page 736.

Haldane, J. S., and Poulton, E. P. (1908), "The Effects of Want of Oxygen on Respiration", *The Journal of Physiology*, Volume XXXVII, page 390. Haldane, J. B. S. (1921), "Experiments on the Regulation of the Blood's Alkalinity", *The Journal of Physiology*, Volume LV, page 265.

Herxheimer, H. (1946), "Hyperventilation Asthma", *The Lancet*, Volume I, page 83.

Hinshaw, H. C., Rushmer, R. F., and Boothby, W. M. (1943), "The Hyperventilation Syndrome and its Importance in Aviation", *The Journal of Aviation Medicine*, Volume XIV, page 100.

Hollo, J., and Weiss, S. (1924), *"Alkalische Verschiebung der Blutreaktion bei basedowscher Krankheit"*, *Klinische Wochenschrift*, Volume III, Part II, page 1632; *"Über extravasale Änderungen der Blutreaktion des Menschen"*, *Biochemische Zeitschrift*, Volume CLVIII, page 211.

Jackson, J. Hughlings (1884), "Evolution and Dissolution of the Nervous System", *British Medical Journal*, Volume I, pages 591, 660 and 703.

Jones, M. S., and Scarisbrick, R. (1941), "A Comparison of the Respiration in Patients with Effort Syndrome and in Normal Subjects", *Proceedings of the Royal Society of Medicine*, Volume XXXIV, page 549.

Kerr, W. J., Dalton, J. W., and Gliebe, P. A. (1937), "Some Physical Phenomena Associated with the Anxiety States and their Relation to Hyperventilation", *Annals of Internal Medicine*, Volume II, page 961.

Koenig, H., and Groat, R. A. (1945), "Effects of Lowering the Blood pH on Excitability of the Nervous System", *The Journal of Neurophysiology*, Volume VIII, page 267.

Kuntz, A. (1945), "The Autonomic Nervous System", Third Edition.

Landis, E. M., Long, W. L., Dunn, J. W., Jackson, C. L., and Meyer, U. (1926), "Effects of Hot Baths on Respiration, Blood and Urine", *The American Journal of Physiology*, Volume LXXVI, page 35.

Lawrence, R. D., and McCance, R. A. (1930), "Tetany after Exercise", *British Medical Journal*, Volume II, page 245.

Maytum, C. K. (1938), "Sighing Dyspnœa: A Clinical Syndrome", *Journal of Allergy*, Volume X, page 50.

Maytum, C. K., and Willius, F. A. (1934), "Abnormal Respiration of Functional Origin", *Proceedings of the Staff Meetings of the Mayo Clinic*, Volume IX, page 308.

McCance, R. A., and Watchorn, E. (1937), "Overbreathing Tetany", *The Lancet*, Volume I, page 200.

McLean, F. C., and Hastings, A. B. (1935), "Clinical Estimation and Significance of Calcium-ion Concentrations in the Blood", *The American Journal of the Medical Sciences*, Volume CLXXXIX, page 601.

O'Donovan, D. K. (1942), "Hyperventilation Tetany", *The Irish Journal of Medical Science*, Volume CCIV, page 616; (1943), "The Hyperventilation Syndrome", *ibidem*, Volume CCV, pages 519 and 564.

Opit, L. (1943), "A Case of Periodic Convulsions with Hyperventilation Syndrome Base and Some Consideration of the Syndrome", THE MEDICAL JOURNAL OF AUSTRALIA, Volume II, page 336.

Sargant, W. (1940), "The Hyperventilation Syndrome", *The Lancet*, Volume I, page 314.

Schultzer, P., and Lebel, H. (1939), "Spontaneous Hyperventilation Tetany", *Acta medica Scandinavica*, Volume CI, page 303.

Scott, J. W., and Cantor, M. M. (1933), "Spontaneous Hyperventilation Tetany", *The American Journal of the Medical Sciences*, Volume CLXXXVI, page 509.

Silberberg, M. D. (1942), "Sighing Dyspnœa and the Hyperventilation Syndrome", THE MEDICAL JOURNAL OF AUSTRALIA, Volume II, page 38.

Soley, M. H., and Shock, N. W. (1938), "The Etiology of Effort Syndrome", *The American Journal of the Medical Sciences*, Volume CXCVI, page 840.

Spillane, J. D. (1940), "Observations on Effort Syndrome", *British Medical Journal*, Volume II, page 739.

Stead, E. A., junior, and Warren, J. V. (1943), "Clinical Significance of Hyperventilation: The Role of Hyperventilation in the Production, Diagnosis and Treatment of Certain Anxiety Symptoms", *The American Journal of the Medical Sciences*, Volume CCVI, page 183.

Talbott, J. H., Cobb, S., Coombs, F. S., Cohen, M. E., and Consolazio, W. V. (1938), "Acid-base Balance of the Blood in a Patient with Hysterical Hyperventilation", *Archives of Neurology and Psychiatry*, Volume XXXIX, page 973.

Thompson, W. P. (1943), "The Electrocardiogram in the Hyperventilation Syndrome", *American Heart Journal*, Volume XXV, page 372.

Uihlein, A., and Boothby, W. M. (1942), "Hyperventilation: Its Occurrence Among Passengers on Airplanes", *Proceedings of the Staff Meetings of the Mayo Clinic*, Volume XVII, page 417.

White, P. D., and Hahn, R. G. (1929), "The Symptom of Sighing in Cardiovascular Diagnosis; with Spirographic Observations", *The American Journal of the Medical Sciences*, Volume CLXXVII, page 179.

Wingfield, A. (1941), "Hyperventilation Tetany in Tropical Climates", *British Medical Journal*, Volume I, page 929.

Wood, P. (1941), "Da Costa's Syndrome", *British Medical Journal*, Volume I, pages 767, 805 and 845.

TOXICITY OF DRUGS USED IN LOCAL ANÆSTHESIA, WITH THE REPORT OF A FATAL CASE.

By J. F. McCULLOCH, M.B., Ch.M., M.R.A.C.P.,

Sydney.

PERIODICALLY a death or "near miss" follows the use of a particular drug for local anæsthesia. Almost all the substances ever used for this purpose have been incriminated at one time or another, if we leave aside the disastrous cases in which one drug has been mistaken for another more toxic, owing to a similarity in name. The substitution of cocaine for procaine, or "Percaine"—now "Nupercaine"—for procaine provide melancholy evidence of the fallibility of human nature. A sudden death, difficult to explain, occurred in my practice recently and seems worth recording.

Report of a Case.

The patient was a male, aged twenty-eight years, suffering from advanced bilateral pulmonary tuberculosis. A phrenic crush and pneumothorax had been unsuccessfully attempted, and at a conference held by members of the chest unit of the hospital, it was decided that thoracoplasty should be done.

Five weeks previously this patient had had the first stage satisfactorily performed, with the use of the technique shortly to be described. On the second occasion events marched as follows. The patient had been given "Omnopon" (two-thirds of a grain) and scopolamine (one one-hundred-and-fiftieth of a grain) one hour before anæsthesia was to be commenced. He arrived in the operating theatre very drowsy, but conscious and quite cooperative. He was thin and gaunt, but otherwise his condition was fairly good.

The usual procedure in these cases had been to perform a brachial plexus block, a paravertebral block of the upper nine spaces and a local infiltration of the skin and underlying structures in the region of the incision. The anæsthetic solution was a mixture of procaine (one in 200) and "Nupercaine" (one in 4000), with three minims of adrenaline (one in 1000) to the ounce.

The brachial plexus block had been finished and the patient turned on his side to allow the rest of the performance to proceed. The first three paravertebral spaces were injected, ten millilitres of the solution being used to each space. The patient then seemed quiet and slightly livid in colour, but answered questions and said he felt all right. Two more spaces were injected, the total amount of the anæsthetic fluid given being 90 millilitres, containing less than 25 milligrammes of "Nupercaine" and under 0·5 gramme of procaine. The patient was then unconscious and died shortly after. Tracheal intubation and inflation with oxygen were performed at once, as well as cardiac massage and the injection of 0·5 millilitre adrenaline (one in 1000) into the myocardium. All these measures failed.

Post-mortem examination revealed advanced pulmonary tuberculosis with cavitation in both lungs and a pale, flabby myocardium, but nothing else of significance.

Discussion.

In every medical and dental community there are practitioners who, because of a bad fright, have eschewed the use of some particular drug for local anæsthesia. No unanimity exists as to which is the safest, one man using nothing but "Decicain", another cocaine, and another procaine. Much, of course, depends on whether the drugs are used for topical application or injection. Whatever the means of introduction into the body, there seems to be the risk of some imperfectly understood toxic effects with each of the drugs mentioned, as well as with many others, including "Nupercaine" and "Metycaine". Procaine admittedly is the least toxic of all, but also the least effective, particularly for surface anæsthesia.

In a recent analysis of sudden deaths (Richards, 1947) there were 32 due to anæsthesia, and of these two followed throat spraying with "Decicain" for bronchoscopy. It is a surprising fact that of all the deaths reported following the use of some local anæsthetic agent, a large proportion at least result from surface application. In this regard it must be admitted that the use of large amounts of solutions of any agent for topical anæsthesia is to be condemned strongly. It is easy to imagine that pledgets of cotton wool dripping wet with a 5% solution of cocaine may well be more injurious than those tightly squeezed from a 20% solution of cocaine. In the case reported, the cause of death was obviously an effect on the cardio-muscular system or the respiratory system, or on both, but the reason for it seems a little obscure.

The following points are of interest: (*a*) A precisely similar anæsthetic had previously been given to this patient with no ill-effects. (*b*) A small proportion only of the total amount of anæsthetic agent had been injected on the second occasion, and at six different sites. (*c*) Death was extremely sudden and not preceded by any convulsive seizure or evidence of restlessness.

There would seem to be four possible causative factors:

1. Intravenous injection. Such a possibility must always be taken into consideration when injections are being made near big vessels. In this case, as always, the piston of the syringe was withdrawn several times during the emptying of each barrelful. The largest amount of anæsthetic solution injected at any one site was 40 millilitres (into the brachial plexus area). This would contain 10 milligrammes of "Nupercaine" and 200 milligrammes of procaine. Goodman and Gilman (1941), while stressing the high toxicity of "Nupercaine" (five times greater than that of cocaine) and its great anæsthetic potency, recommend its use subcutaneously in strengths varying from one in 2000 to one in 1000; they suggest a limit of 100 millilitres (100 milligrammes) of the latter strength, and report a death after 135 milligrammes given subcutaneously. There seems to be no information available as to the lethal intravenous dose in human beings. In a case reported by Organe (1942) a patient died after the injection of about 250 milligrammes in a solution of slightly more than one in 1000 strength, for a subcostal field block. In this case also the patient had been given an injection of a similar preparation a few days previously, for an appendicostomy. The amount was unstated, but was probably less than the dose which subsequently caused death. In this case, however, there were generalized convulsions lasting for several minutes. The dose of "Nupercaine" has been given by Ciba, Limited, quoted by Organe, as two to three milligrammes per 16 kilograms of body weight, varying with the dilution. If the amount of 2·5 milligrammes is taken as an average, this would allow 15 millilitres per stone of body weight of the one in 1000 preparation, or 60 millilitres of the one in 4000 preparation. If my patient is assumed to have weighed nine stone, this allows 540 millilitres in all, at least four times as much as the amount used.

Death or lesser toxic manifestations have also been known to follow the spraying of a patient's throat with a solution of 2% "Nupercaine" (Titche and Crays, 1943) as a preparation of bronchoscopy (H. J. Daly). Whatever the drug employed, a strict limit on the total amount used as throat spray seems a wise precaution. Thus 2·0 millilitres of 2% "Decicain" solution with one millilitre each of distilled water and adrenaline (one in 1000) make a preparation which gives admirable pharyngeal and laryngeal anæsthesia if properly used, with so far a minimum of side-effects.

2. Intrathecal injection. Intrathecal injections undoubtedly have been made inadvertently during the use of drugs for local anæsthesia in the vicinity of the vertebral bodies. It would seem unlikely, however, that any lateral prolongation of the theca could be entered by a needle introduced one centimetre from the mid-line and directed forwards and upwards. In any case, the amount introduced in any one space would be very small (2·3 milligrammes of "Nupercaine" and 50 milligrammes of procaine) and not sufficient to cause sudden death.

3. Sensitization by the previous injection. The word idiosyncrasy has, in the past, been used to cover a number of imperfectly understood pharmacological reactions. It is defined by Goodman and Gilman as an abnormal or unusual response to a drug. They state, further, that it may occur after small doses or after a drug has been administered for the first time, or it may suddenly appear during an uneventful course of medication. They do not mention any particular group of drugs, but it is generally recognized that sera and drugs used for local anæsthesia are peculiarly productive of unpleasant surprises in this regard, whatever may be the exact mechanism.

In regard to the group of drugs used for local anæsthesia, a number are closely related chemically, some being benzoic acid esters, such as cocaine, "Stovaine" and "Metycaine", or para-amino benzoic acid esters like procaine and "Decicain". An astonishing fact is that "Nupercaine", five times more toxic than cocaine, but also much more potent and of longer duration, is totally unrelated to any of the above, being a quinoline derivative.

Doane and Cohn (1945) report 19 cases collected from various sources, in which the instillation of 2% "Pontocaine" solution caused toxic reactions fatal in nine of the cases. The 10 other patients recovered after intravenous barbiturate therapy. This is a very serious state of affairs, considering how common such a procedure is.

Although "Pontocaine" and "Decicain" are described in pharmacology books as being identical, an experienced ear,

nose and throat surgeon (M. Coutts) states categorically, after a wide experience with the latter drug, that he has never seen a toxic reaction with its use in ten years, but that he had sufficient frights with the former during a year's use, when the other was unprocurable, to convince him that there was some very sinister difference between them.

It is possible that a patient may be sensitized to the effect of a drug by a previous injection—something in the nature of an antigen-antibody response. In the case reported above, this is a distinct possibility. A similar case has been reported (Ahroon, 1946). In this a woman died after having a 2% solution of "Tetrocaine" ("Decicain", "Pontocaine" and "Amethocaine" are all synonyms) sprayed on her throat and instilled into her larynx. Not more than four millilitres in all were used, containing 80 milligrammes of the drug. As an amount of 200 to 300 milligrammes of "Amethocaine" has been commonly used in anæsthesia for gastric surgery, this amount seems little enough. In the case reported by Ahroon, the patient had had a similar anæsthetic entirely without incident ten days previously. What is so surprising is the small quantity of the anæsthetic solution which had been injected; several convulsions occurred in a short time followed by death, in spite of the intravenous injection of sodium phenobarbital.

If this was the case, it would be most important to determine which patients were sensitive to such drugs. There is evidence to suggest that those having a history of allergy, familial or personal, are more liable to reactions with substances used for local anæsthesia. It has been further suggested that the use of procaine may sensitize a patient to "Decicain", which has a closely related chemical formula.

4. Wrong preparation. There is always a remote possibility, in cases of sudden death, that a wrong solution has been injected. In this case, sealed ampoules both of "Nupercaine" and of procaine were used with labels etched on the glass, and each label was checked. Appropriate dilutions were made with distilled water. In any case, analysis of the remaining solution confirmed their correctness.

In view of the increasing importance of regional anæsthesia and its great value in so many surgical procedures, these facts offer food for disturbing thought.

References.

Richards, R. (1947), "A Note on the Causation of Sudden Death", *British Medical Journal*, Volume II, page 51.
Goodman, L., and Gilman, A (1941), "The Pharmacological Basis of Therapeutics", page 302.
Organe, G. (1942), "Convulsions Following 'Percaine' Local Anæsthesia", *The Lancet*, Volume II, page 33.
Titche, L. L., and Crays, W. H. (1943), "Toxic Reaction to "Nupercaine", *Annals of Otology, Rhinology and Laryngology*, Volume LII, page 202.
Daly, H. J., personal communication.
Doane, J. C., and Cohn, E. M. (1945), "The Toxic Effect of 'Pontocaine' Employed Locally", *Anesthesiology*, Volume VI, page 421.
Coutts, M., personal communication.
Ahroon, W. (1946), "Report of a Death from 'Pontocaine Hydrochloride', *The Laryngoscope*, Volume LVI, page 320.

A CASE OF THE SCHÖNLEIN–HENOCH SYNDROME.

By J. ALLSOP,
Medical Registrar, Royal Prince Alfred Hospital,
and
K. VINER SMITH,
Senior Lecturer in Pathology, University of Sydney.

SEVERAL workers have in recent years attempted to advance our knowledge of *periarteritis nodosa*, Schönlein-Henoch purpura and related vascular diseases.

Gairdner (1948) has reviewed the condition known as anaphylactoid purpura, or the Schönlein-Henoch syndrome. By a study of cases and of the literature he has been able to clarify both the clinical and pathological picture.

This case is reported as it is considered that, with other case reports, it may assist in a critical evaluation of the opinions of these various workers.

Clinical History.

The patient was a man aged thirty years. He was a tram conductor. All his life he had enjoyed good health, apart from an attack of rheumatic fever at fourteen years of age. He gave no account of any past allergic manifestations, such as asthma, hay fever, eczema or urticaria. He had at no time prior to admission to hospital been treated with sulphonamides.

Three weeks before his admission to hospital, without any prior sore throat or cold, he began to experience colicky abdominal pain centred about the umbilicus. He became nauseated and vomited bile-stained fluid. This pain and vomiting came in attacks lasting several hours, the attacks passing off without being influenced by any treatment. After about five days this pain abated and he became subject to diarrhœa; the stools were of a normal colour at first, but later became very dark. He thought that there was blood in them. This diarrhœa lasted three days.

A few days later he noticed that his ankles were becoming painful and swollen, especially on walking. Similar pain and swelling then appeared in his knees, wrists and elbows, in that order. All joints remained swollen and sore.

Three days before his admission to hospital he noticed a purple rash on his forearms. Within a short time this rash spread to his hands, face, abdomen, legs and feet.

No other relevant facts were obtained from his family or environmental history.

On physical examination he was found to be a stockily built man, moderately at ease, pale, perhaps somewhat puffy, with a conspicuous rash on forearms, hands, abdomen, buttocks, legs, feet, and on the face around the nose. The rash was most heavily distributed on the extensor surfaces of the limbs. It had the features of a purpuric eruption, some of the hæmorrhages being quite 0·5 centimetre in diameter.

The ankles, knees and wrists were tender and painful to move. They were swollen with mainly periarticular œdema; but a patellar tap could be elicited on both sides. The elbows were painful, but not swollen. Subcutaneous pretibial œdema was present on both sides.

There were no buccal hæmorrhages and his ocular fundi were normal. No visceral or glandular enlargement could be felt. Hess's tourniquet test repeatedly gave a negative response. The systolic blood pressure was 150 and the diastolic pressure was 90 millimetres of mercury; the temperature was 100·5° F. and the pulse rate 120 per minute. The urine contained one quarter of albumin.

Laboratory investigations gave the following results.

The hæmoglobin value was 11·2 grammes *per centum* (= 76% normal). The red blood cells numbered 3,670,000 per cubic millimetre. The colour index was 1·01. The mean corpuscular volume was 92 cubic microns. The mean corpuscular hæmoglobin value was 30 micromicrogrammes. The mean corpuscular hæmoglobin concentration was 32% (normal). The hæmatocrit reading was 34% packed red cells. A blood film showed anisocytosis of red cells.

The leucocytes numbered 12,150 per cubic millimetre; 84% were neutrophile cells, 10% were lymphocytes, 5% monocytes, 1% eosinophile cells. At no stage was eosinophilia present.

The platelets numbered 257,000 per cubic millimetre. The bleeding time, coagulation time, prothrombin time, fragility and sedimentation rates were normal.

The blood was sterile on culture and also on repeated culture.

A centrifuged deposit from the urine contained five to ten red cells per high-power field; there were a moderate number of cellular casts.

From a throat swabbing hæmolytic streptococci of group A were grown in mixed culture.

The electrocardiogram was normal; the *P-R* interval was 0·17 second.

After the patient's admission to hospital his illness took a different turn. The florid purpuric rash faded and, apart from one further crop developed a few days after admission, was not again seen. The joint swelling subsided and although the patient complained of vague aches and pains in his joints from time to time, no gross manifestations recurred. Abdominal colic continued to trouble him intermittently with episodic diarrhœa. The outstanding features of the malady were now progressive renal involvement, continued fever of 99° to 101° F., constant tachycardia of 110 to 120 per minute, and the development of a new type of rash.

The renal disorder was shown by: increasing œdema, one stone in weight being gained; constant albuminuria of one-half to one-quarter shown by ward test; progressive hæmaturia with up to 40 red cells per high-power field of centrifuged deposit; the constant presence of cellular granular and hyaline casts; sustained hypertension with a systolic blood pressure of 160 and a diastolic pressure of 100 millimetres of mercury; impaired renal function and a drop in plasma protein. The blood urea level on the patient's admission to hospital was 108 milligrammes per 100 millilitres; four days before death it was 114 milligrammes *per centum*; the blood cholesterol content was 125 milligrammes *per centum* and the serum protein content was 4·65 grammes *per centum*. The specific gravity of the urine was fixed at about 1010. Urinary output did not fall, varying between 30 and 70 ounces per day.

About ten days before his death the patient developed an itchy, maculo-papular, pink to brownish rash on the back of the forearms and hands; this persisted till his death.

A few days before his death he became breathless. A gallop rhythm was detected at the apex with some enlargement of the heart. Râles appeared at the lung bases. An electrocardiogram at this stage showed flattened *T* waves in lead 1 and the *P-R* interval was 0·15 second.

He died in an attack of acute pulmonary œdema after a period of twenty-five days in hospital.

The drugs he received included, at various times, "Benadryl", "Rutin", penicillin by intramuscular injection and in the form of lozenges.

Autopsy Report.

An autopsy was performed thirty-six hours after death. The body was obese.

On the skin of each forearm, especially on the extensor surface, there were numerous nodules about five millimetres in diameter and raised a little above the surrounding skin surface. The lungs were œdematous. The heart, including the valves, appeared normal. The spleen was large (350 grammes) and firm. The surface of the liver was a little wrinkled and the organ was pale. No significant change was found in the gall-bladder or bile ducts. The kidneys were large and pale. The right kidney weighed 310 grammes and the left 300 grammes. The capsules stripped easily. On section the cortex was found to be wide and pale.

The œsophagus, stomach and duodenum appeared normal. In the small intestine there were numerous areas, one to three centimetres long, in which the mucosa was darkened, possibly by old hæmorrhage. The large intestine, pancreas, adrenal glands, urinary bladder and testes appeared normal. The brain was not examined.

Tissue for microscopic study was taken from a kidney, one of the dark areas of the small intestine, a skin nodule, the spleen, the heart, the liver and a pectoral muscle. Sections were stained by hæmatoxylin and eosin, Masson's trichrome stain, Van Gieson's stain, Verhoeff's elastic stain and Weigert's fibrin stain.

In the skin nodule the striking feature was the presence of collections of neutrophile polymorphonuclear leucocytes and cells resembling histiocytes in the superficial layer of the corium (Figure I). These collections were mainly around capillaries, but were also around small arterioles. No histological changes were seen in the vessel walls. In these areas the normal collagen fibres of the corium appeared to have been destroyed or displaced. Over the part of the corium most affected the epidermis had become thickened by swelling of its cells.

In the kidney similar collections of cells with some eosinophile polymorphonuclear leucocytes were seen around some arterioles in the cortex and around some congested capillaries and arterioles in the medulla. However, there was no visible necrosis in the vessel walls. Also, in about half the glomeruli, areas of necrosis were seen involving up to a quarter of the glomerulus (Figure II). Some polymorphonuclear leucocytes were seen in the affected glomeruli.

Throughout the wall of the small intestine there was an infiltration of inflammatory cells comprising neutrophile and eosinophile polymorphonuclear leucocytes and histiocytes, most marked in the submucosa. Here the cells were concentrated around some of the arterioles and small arteries. Among some of these perivascular collections of cells there was seen some necrotic material. With hæmatoxylin and eosin stain this material resembled fibrin; but it failed to stain with Weigert's fibrin stain. The blood vessels in these areas were affected in different ways. Inflammatory cells could be seen in the walls of some, splitting the coats apart; in others there was a hyaline change in the wall; and in others there was evidence of necrosis involving the media and intima (Figures III, IV and V). Some vessels had aneurysms and a few had ruptured. Some other blood vessels were dilated and thin-walled with no signs of inflammation or necrosis.

In the sections of liver, heart and pectoral muscle perivascular inflammation was present, but much less extensive and less severe than in the skin, kidney or small intestine. In the spleen there was congestion and some degenerative changes in the blood vessels of the Malpighian corpuscles. A number of polymorphonuclear leucocytes, mainly eosinophile, are present in the lymphoid tissue.

In all the tissues which exhibited the perivascular changes described above similar changes were seen in areas where no blood vessels were visible. From the distribution and frequency of this appearance it is assumed that the reaction in these cases was in relation to a blood vessel which is not in the plane of section.

Discussion.

This case corresponds closely, in both clinical and pathological aspects, to Gairdner's (1948) picture of the Schönlein-Henoch syndrome.

The skin at first developed a purpuric rash, and when this had faded a red maculo-papular rash appeared on the extensor surface of each forearm and on the dorsum of the hands; the colour later changed to brown. This second rash is, according to Gairdner, typical of the disease. The histological changes were those of an acute inflammatory reaction around the small blood vessels.

The gastro-intestinal symptoms and signs were colic, vomiting, diarrhœa and blood in the stools. The bowel lesion at autopsy was found to be patchy; and the microscopic features were of the same nature as those seen in the skin, but were more severe and there was necrosis of the vessel walls. Eosinophile polymorphonuclear leucocytes were present in the inflamed areas. Vessels up to the size of small arteries were affected; Gairdner considers that arterioles are the largest vessels affected. The difference here is possibly one of terms rather than of fact.

There was clear evidence of kidney disease, including hæmaturia. The final phase of the illness was characterized by renal failure associated with hypertension. The actual mode of death was acute pulmonary œdema following acute left ventricular failure, such as may be seen in acute glomerulo-nephritis. The kidney lesion was a focal glomerulo-nephritis in which necrosis was a more prominent feature than inflammatory reaction. Gairdner notes that clinically the renal disease resembles the usual forms of glomerulo-nephritis. Histologically, however, he found in the literature varying reports including both diffuse and focal lesions.

Many joints were swollen and painful from time to time. There was a moderate degree of anæmia with a mild neutrophilia. In all these features our case is in substantial agreement with Gairdner's description.

Several facts may have a bearing on the ætiology of the condition. From a throat swab taken soon after the patient's admission to hospital hæmolytic streptococci of group A were grown in a mixed culture; and the patient had suffered from rheumatic fever at the age of fourteen years. Gairdner observed two cases in which rheumatic fever and the Schönlein-Henoch syndrome had both occurred in one subject; and he found one other case in the literature. Infection with a hæmolytic streptococcus of group A is recognized as a frequent occurrence in both these conditions (Gairdner, 1948, and Swift, 1947).

Zeek *et alii* (1948) discuss the pathology of "hypersensitivity angiitis", a condition which includes the sulphonamide sensitivities and, from Gairdner's description, we consider the Schönlein-Henoch syndrome. The lesions correspond closely with the case described in the present contribution.

Zeek *et alii* (1948) describe the vascular lesions in hypersensitivity angiitis as an acute inflammatory process occurring in the walls of vessels up to the size of small arteries. They consider that the lesions are of about the same age in any one case; that there is no evidence of any attempt at healing; that the lesions occur in the spleen, both in the follicular arterioles and in the vessels of the trabeculæ, and in the lung. In all their cases they found an unusual type of glomerulo-nephritis in which necrosis and exudation were the main lesions. They contrast the lesions with those found in *periarteritis nodosa*. In *periarteritis nodosa* they say the vessels which are affected vary in size from arterioles to arteries; the inflammatory process is at different stages in any one case; there is always early fibrosis and the formation of new capillaries in some of the lesions; and the vessels of the lung and the spleen are not affected. In those cases in which the kidneys are diseased the lesions are those of the usual diffuse glomerulo-nephritis. Gairdner (1948) is at variance with these authors in that he believes Schönlein-Henoch purpura and *periarteritis nodosa* are essentially the same disease.

If the conclusions of Zeek and his co-workers (1948) are accepted (and they are open to some criticism), the experimental work of Rich and Gregory (1943) and of Hopps and Wissler (1946) must be reviewed.

Rich and Gregory (1943), by injections of horse serum into rabbits, produced clinical signs of hypersensitivity and pathological lesions which they considered were those of *periarteritis nodosa*. Hopps and Wissler (1946) repeated this work and confirmed the main findings. Other workers have reported many cases of sulphonamide sensitivity (Lichtenstein and Fox, 1946; French, 1946; More *et alii*, 1946; Durie and Brodziak, 1948) and have noted that the lesions resemble those of *periarteritis nodosa*.

Careful examination of the descriptions and photographs of the lesions recorded by all these authors strongly suggests that these lesions fall into the class of hypersensitivity angiitis rather than that of *periarteritis nodosa* by the criteria of Zeek *et alii*.

All this work suggests that the Schönlein-Henoch syndrome is a sensitivity reaction; and the frequent presence of a hæmolytic streptococcus of group A suggests that this organism is in some way responsible, at least in many cases. Study of the pathology of sulphonamide sensitivity shows that the lesions differ in degree rather than in nature from those of the Schönlein-Henoch syndrome.

Summary.

1. A case illustrating the Schönlein-Henoch syndrome is described.

2. The experimental work bearing on its ætiology is reviewed.

3. The lesions found in this condition are compared with those found in hypersensitivity angiitis.

Acknowledgements.

We wish to thank Dr. T. M. Greenaway for permission to publish this report and for many helpful suggestions; and Professor W. K. Inglis, Dr. J. Halliday and Dr. G. F. Davies for advice on many aspects of the case.

The excellent microphotographs were taken by the Department of Medical Artistry of the University of Sydney.

References.

Durie, E. B., and Brodziak, I. A. (1948), "Necrotizing Vascular Lesions Believed to be Due to Hypersensitivity to Sulphadiazine", THE MEDICAL JOURNAL OF AUSTRALIA, Volume I, page 710.

French, A. J. (1946), "Hypersensitivity in the Pathogenesis of the Histopathologic Changes Associated with Sulfonamide Chemotherapy", *The American Journal of Pathology*, Volume XXII, page 679.

Gairdner, D. (1948), "The Schönlein-Henoch Syndrome (Anaphylactoid Purpura)", *The Quarterly Journal of Medicine*, Volume XVII, New Series, page 95.

Hopps, H. C., and Wissler, R. W. (1946), "The Experimental Production of Generalised Arteritis and Periarteritis (Periarteritis Nodosa)", *The Journal of Laboratory and Clinical Medicine*, Volume XXXI, page 939.

Lichtenstein, L., and Fox, L. J. (1946), "Necrotising Arterial Lesions Resembling those of Periarteritis Nodosa and Focal Visceral Necrosis following Administration of Sulphathiazole", *The American Journal of Pathology*, Volume XXII, page 665.

More, R. H., McMillan, G. C., and Duff, G. L. (1946), "The Pathology of Sulfonamide Allergy in Man", *The American Journal of Pathology*, Volume XXII, page 703.

Rich, A. R., and Gregory, J. E. (1943), "The Experimental Demonstration that Periarteritis Nodosa is a Manifestation of Hypersensitivity", *Johns Hopkins Hospital Bulletin*, Volume LXXII, page 65.

Swift, H. F. (1947), "Rheumatic Fever" in Cecil's "Textbook of Medicine", Seventh Edition, page 171.

Zeek, P. M., Smith, C. C., and Weeter, J. C. (1948), "Studies on Periarteritis Nodosa. III: The Differentiation between the Vascular Lesions of Periarteritis Nodosa and of Hypersensitivity", *American Journal of Pathology*, Volume XXIV, page 889.

Legends to Illustrations.

FIGURE I.—Skin—perivascular inflammation is evident. A small area of epidermis is visible in the top left corner. (× 400.)

FIGURE II.—Kidney—a typical glomerular lesion. (× 400.)

FIGURE III.—Small intestine—the submucosa is greatly thickened by an inflammatory reaction. This is most intense around the blood vessels. (× 50.)

FIGURE IV.—Small intestine—submucosa. Portion of Figure III is here shown under higher magnification to demonstrate the perivascular reaction and the necrosis of the vessel walls. (× 200.)

FIGURE V.—Small intestine—showing an affected arteriole. (× 400.)

THE USE OF URETHANE IN LEUCHÆMIA.

By IAN COLLINS,
Royal Prince Alfred Hospital, Sydney.

Review of Literature.

URETHANE (ethyl carbamate $NH_2COOC_2H_5$) has been known for many years. It has been used in experimental physiology as a hypnotic for cats, and in surgery, together with quinine, as a sclerosing agent for varicose veins.

In 1946 Haddow and Sexton noticed a depression of the leucocyte count while experimenting with esters of carbamic acid in the treatment of experimental tumours in animals. This suggested the trial of urethane in patients with leuchæmia.

In May, 1946, Paterson *et alii* reported the use of urethane in the treatment of thirty-two patients with leuchæmia. The drug was given orally, the dose being 3·0 to 4·0 grammes daily. Nineteen of their patients had myeloid leuchæmia; of these, ten were benefited. Their results for lymphatic leuchæmia were less satisfactory. In the myeloid group a control series of patients was treated with deep X-ray therapy. The results with urethane were found to be approximately as satisfactory as in the group treated with X rays. The white cell counts dropped, the hæmoglobin value rose and the splenic outline decreased. Similar clinical remissions occurred in the two series. In the lymphatic group enlarged lymph nodes diminished in size but did not disappear.

Toxic effects produced by the urethane were not as a rule very severe. They comprised nausea and vomiting, with slight drowsiness in one case. In two cases serious depression of the marrow occurred, although the drug as a rule depressed the white rather than the red cell count.

ILLUSTRATIONS TO THE ARTICLE BY Dr. J. ALLSOP AND Dr. K. VINER SMITH.

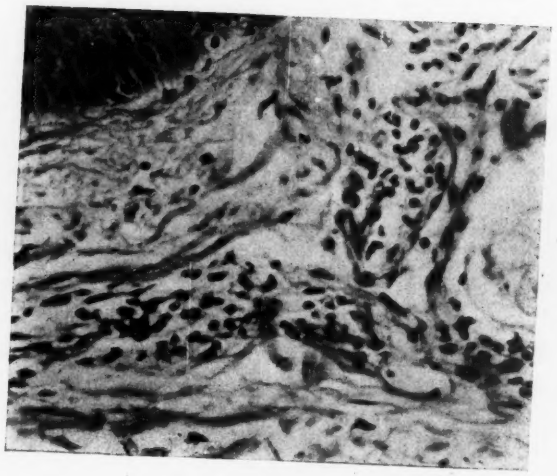

Figure I.

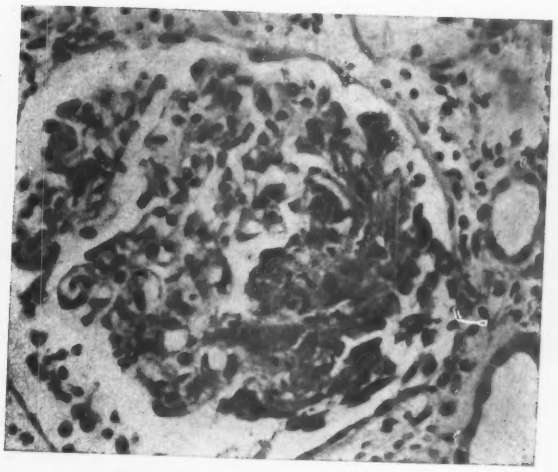

Figure II.

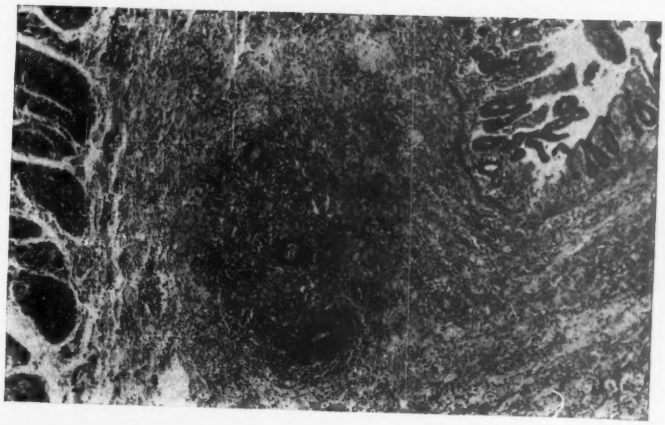

Figure III.

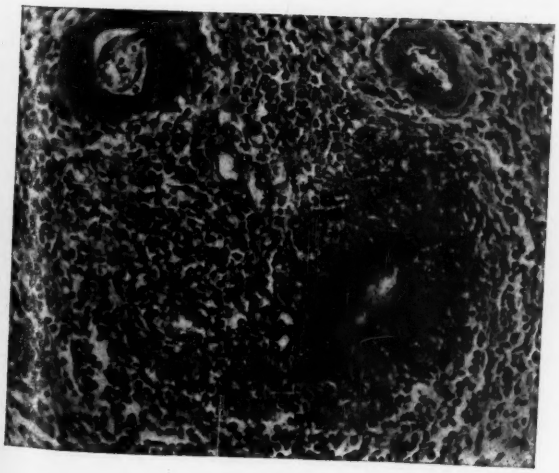

Figure IV.

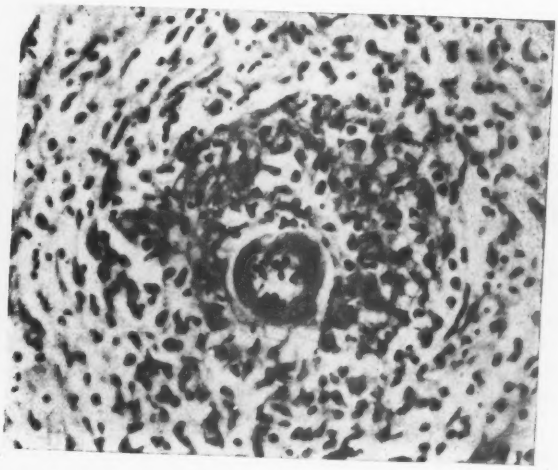

Figure V.

ILLUSTRATIONS TO THE ARTICLE BY DR. IAN COLLINS.

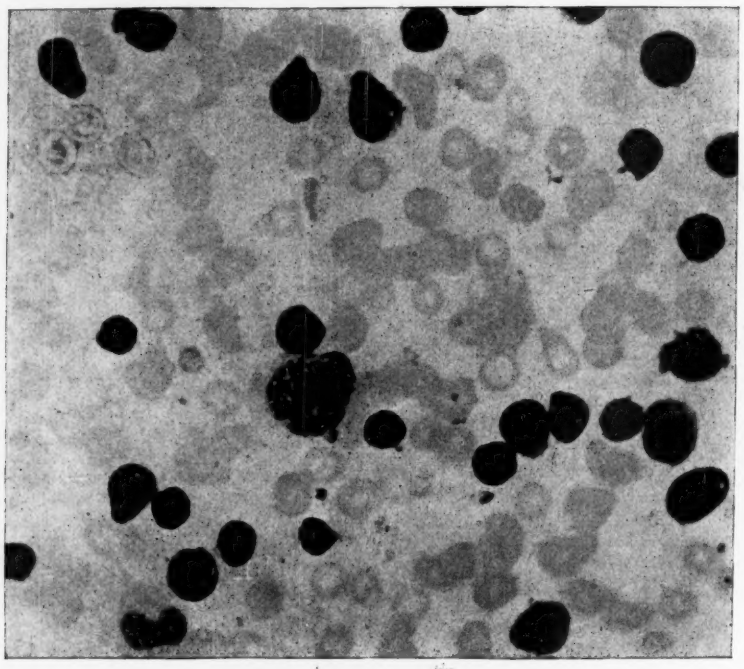

FIGURE IV.

Sternal marrow (Case III). Practically all the nucleated cells present are lymphocytes. This film was taken after a long period of urethane therapy, and indicates the lack of effectiveness of this therapy in this case. Urethane was suspended as a result of its failure to affect the overwhelming preponderance of lymphocytic cells in the marrow.

ILLUSTRATIONS TO THE ARTICLE BY DR. GILBERT PHILLIPS.

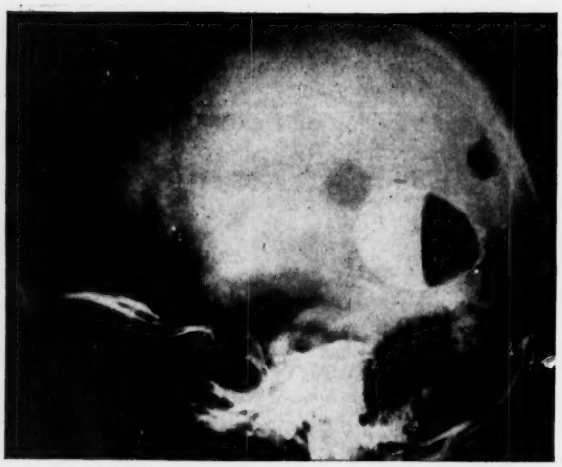

FIGURE II.

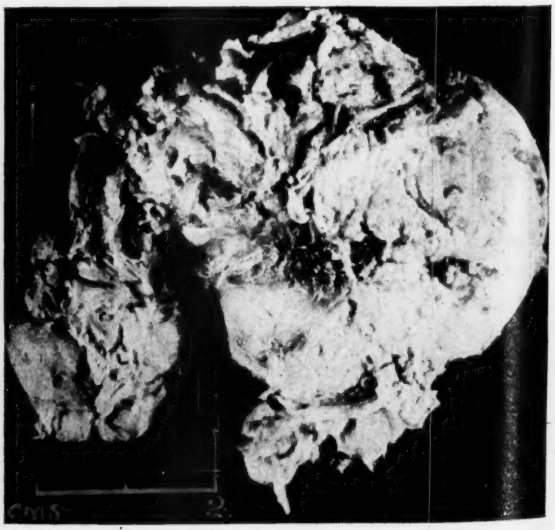

FIGURE III.

More recent studies from America confirm the results of Paterson. Creskoff *et alii* (1948) employed the drug in the treatment of twenty-four patients, seven suffering from chronic myeloid leuchæmia, seven from chronic lymphatic leuchæmia, and ten from acute leuchæmia of various types.

In the myeloid series four of their patients were in the terminal stages of the disease and the results were bad. In the other cases the results were for the most part good. One patient conceived while under treatment and was last reported as well towards the end of her pregnancy. The results with lymphatic leuchæmia were good in two cases, but bad in the remainder. In acute leuchæmia no benefit was obtained. The toxic effects were nausea, mild or severe, and sometimes drowsiness. In two cases depression of the marrow occurred. The authors were of the opinion that in many cases of chronic myeloid leuchæmia the drug had a good palliative effect. In other cases, however, the fall in the leucocyte count was a spurious improvement, the anæmia was unchecked, and the patient's condition progressively deteriorated. They consider that in such cases continued administration of the drug is harmful, and recommend suspension of the drug if clinical improvement does not occur within a week after the fall in the white cell count, or if no satisfactory fall occurs within sixty days from the start of treatment.

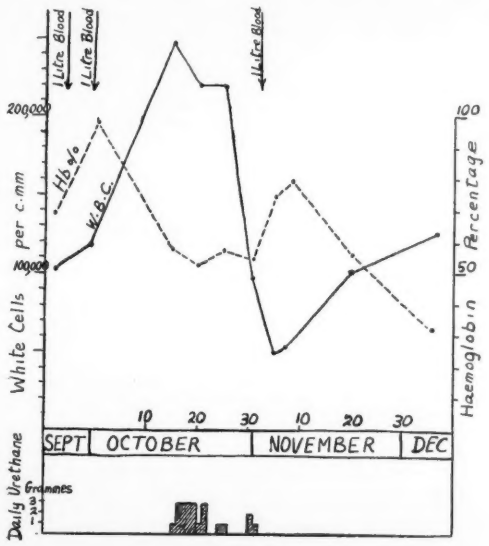

FIGURE I.

Case I. Note fall in leucocyte count after administration of urethane.

In general, the authors consider that urethane is less consistent and satisfactory than deep X-ray therapy. Watkins and others at the Mayo Clinic have presented a similar series with similar results. They recommend (1948) oral use of the drug with an initial dose of three grammes. The primary fall in the leucocyte count usually occurred seven to fourteen days after the institution of therapy and was often preceded by a transient elevation. Sometimes, however, the initial depression was delayed. They recommend reduction of the dose as the count falls, and place the patient on a maintenance dose of 0·5 to 1·0 gramme daily to keep the leucocyte count between 10,000 and 20,000 per cubic millimetre. The drug is suspended if the count falls below 10,000 per cubic millimetre. A satisfactory response to treatment usually occurred within three to ten weeks (average six weeks) after an average administration of 80 grammes. Creskoff and others have been administering urethane intravenously in 200 millilitres of normal saline solution. They have also administered urethane by the rectum, but have found that it causes rectal irritation.

Piney (1947) believes that the drug is best administered by enteric coated tablets. Osgood (1948) believes that deep X-ray therapy is far superior to urethane in the treatment of leuchæmia.

Clinical Trials.

Urethane became available late in 1948 at Royal Prince Alfred Hospital and was employed in such cases of leuchæmia as were available. The following three cases—two of chronic myeloid leuchæmia and one of chronic lymphatic leuchæmia—portray the experiences of one medical unit.

CASE I.—E.T., a female, aged sixty years, developed tiredness and weakness in 1945. In 1946 she was diagnosed as suffering from chronic myeloid leuchæmia. From that time until her final admission to hospital she was treated by deep X-ray therapy and blood transfusions, and had remained in fairly good health. In 1948 her health began to deteriorate, she became more tired and began to lose weight, and took longer to respond to deep X-ray and transfusion therapy. She was admitted to Royal Prince Alfred Hospital on September 22, 1948.

Physical examination revealed an emaciated pale Chinese woman. The spleen was greatly enlarged, extending medially to the umbilicus and downwards almost to the pelvic brim. It was firm, smooth, and tender. The liver was enlarged to one inch below the subcostal margin. No lymphatic glands were palpable. Full blood count on admission revealed 3·57 million red cells per cubic millimetre, a hæmoglobin content of 10·1 grammes *per centum* (69% normal), and 103,000 white cells per cubic millimetre. The differential count was: myeloblasts 15%, premyelocytes 11%, myelocytes 25%, metamyelocytes 7%, neutrophile cells 24%, lymphocytes 1%, eosinophile cells 7%, basophile cells 9%.

TABLE I.

Blood Counts During Deep X-Ray Therapy, Prior to Urethane Administration (Case II).

Date.	Hæmoglobin Percentage.	White Cells per Cubic Millimetre.
10/ 3/47	60	356,000
18/ 3/47	65	241,000
8/ 4/47	72	88,000
29 /4/47	83	100,000
26/ 5/47	88	129,000
24/ 6/47	92	75,000
15/ 7/47	80	16,300
19/ 8/47	85	46,500
1/10/47	80	79,000
3/11/47	94	37,500
10/12/48	85	157,000
20/ 1/48	88	83,000
23/ 2/48	90	15,600
18/ 5/48	100	58,500
22/ 6/48	74	122,000
2/ 8/48	83	6,600
15/ 9/48	78	29,000
11/10/49	75	87,000
29/11/49	85	41,000
13/12/49	68	50,000
12/ 1/49	60	37,000

Several blood transfusions were given, but the patient's general condition remained poor. Pains developed in the ribs and also in the spleen. The deep X-ray therapist was unwilling to give the patient deep X-ray therapy in view of her poor condition and previous sluggish response to it. Urethane therapy was commenced on the evening of October 16, the daily dose being 3·0 grammes. The total duration of urethane therapy and its effect on the blood count are illustrated in Figure I.

After about five days of urethane therapy the patient, who had been nauseated before the commencement of the course, began vomiting the urethane, and soon her nausea was so extreme that she refused to take the drug. On November 1, 1949, the urethane was resumed, at a dosage of 2·0 grammes a day, but within two days the patient was either vomiting the drug or refusing to take it, and the treatment was finally abandoned. In all the patient received and retained approximately 22 grammes of urethane.

The total white cell count, which had risen to 243,000 per cubic millimetre before the urethane was started, began falling, and eighteen days after therapy commenced had reached a level of 48,000 per cubic millimetre. It then began to rise again and by December 4 was 132,000. The patient

gradually became worse, developed œdema, and died on December 10, 1949.

At autopsy, gross enlargement of the spleen was found, with a small infarct. Microscopically, infiltrations of primitive white cells were found in the spleen, liver, lymph nodes and kidney.

CASE II.—M.C., a female, aged thirty years, was admitted to hospital on January 20, 1949, complaining of tiredness of two and a half years' duration.

She was well until early in 1947, when she became increasingly tired and lethargic, and noticed a lump in her abdomen. A blood count was made, and chronic myeloid leuchæmia was diagnosed. The patient was referred to this hospital and was attending the deep X-ray department up till admission. After some treatment with deep X rays she felt quite well and in her normal health. (For blood counts see Table I.) She remained fairly well, apart from slight fluctuations, until about November, 1948, when she became tired and lethargic again. Between November and the time of her admission to hospital, she lost ten pounds in weight. She complained of a dragging pain in her left side, and of bruising. No hæmorrhages had occurred, and there were no swellings apart from the abdomen.

On physical examination, the patient was seen to be a pale emaciated woman, with a yellowish tinged skin. The spleen was very greatly enlarged, of firm consistency, and smooth. There were no glandular swellings or other abnormalities on examination.

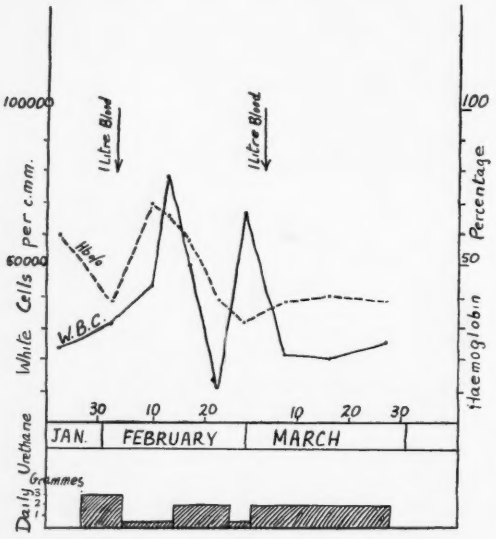

FIGURE II.

Case II. No definite effect can be attributed to urethane.

Laboratory Examinations.—The blood count on her admission to hospital was as follows. The hæmoglobin value was 8·8 grammes *per centum* (60% normal), and the white cell count was 24,000 per cubic millimetre. The differential count revealed 5% myeloblasts, 10% premyelocytes, 12% myelocytes, 18% metamyelocytes, 49% neutrophile cells, 5% lymphocytes, and 10% eosinophile cells.

Progress.—On January 28, urethane was commenced in a dosage of 3·0 grammes daily. This was reduced on February 3 to 0·5 gramme, since the hæmoglobin value had fallen abruptly. On February 14, 1949, the white cell count had risen to 78,000 per cubic millimetre, so the dose was increased to 2·0 grammes daily. Apart from a short interruption, the dosage remained at this level. (See Figure II).

The white cell count varied considerably. It was, on the seventh week, roughly as it had been on the patient's admission to hospital. The only other positive improvement was a slight diminution in the size of the patient's spleen.

The patient's general condition deteriorated greatly after her admission to hospital. The hæmoglobin value showed an extreme tendency to fall, which was checked only by frequent blood transfusion. The patient was severely nauseated by the urethane, which aggravated the discomfort produced by the large spleen. In addition, she experienced several attacks of pain and swelling of the spleen.

From time to time she was troubled by attacks of paroxysmal tachycardia which were at first controlled by "Carbachol" or by quinidine, but finally responded to neither, and were quite capricious in their onset and disappearance. These attacks were shown by the electrocardiograph to be of auricular paroxysmal tachycardia. The patient had never had these attacks before, and it was thought that they were due to irritation of the myocardium by anoxæmia.

During the last week in March the patient developed irregular pyrexia. Attempts were made to sustain her nutrition by oral administration of protein hydrolysates, but her condition continued to deteriorate. She died on March 29, 1949.

At post-mortem examination, the spleen was found to occupy one-third of the abdominal cavity, and was bright red in colour on section. The liver was also very large, but appeared normal. The heart was very small, and showed brown atrophy. Large numbers of myeloid cells were present in the spleen, liver sinusoids and lymph nodes. The bone marrow showed numerous immature myeloid cells.

CASE III.—A.C., a male, aged twenty-five years, was admitted to Royal Prince Alfred Hospital on November 5, 1948, complaining of tiredness and fatigability of six months' duration. He was well until January, 1948, when he suffered a compound fracture of the left humerus. During his convalescence he noticed tiredness, with palpitations and dyspnœa on exertion. These symptoms became worse, and the patient developed attacks of giddiness and sweating, with momentary darkness of the surroundings, but without loss of consciousness.

In spite of a good appetite, he lost one stone in weight in the twelve months before his admission to hospital. He noticed also lumps in the groin and neck. These were not painful, and had not increased greatly in size. There were no relevant previous illnesses.

Physical examination revealed a well-built young man. The face and conjunctivæ were very pale. Small firm glands were palpable in the neck, axillæ and groins. These were not tender or adherent. The spleen was just palpable. No other abnormality was detected on examination.

Progress.—Full blood count on his admission to hospital revealed 2·38 million red cells per cubic millimetre, with a hæmoglobin content of 7·1 grammes *per centum* (48% normal). The white cell count was 19,200 per cubic millimetre, the lymphocytes comprising 81%. No immature cells were seen. Later blood counts revealed similar figures.

Sternal puncture was performed on November 10. The marrow contained very large numbers of small lymphocytes (96% of nucleated cells).

An inguinal lymph gland was removed for biopsy on the same day. Histological examination was not helpful, revealing only sinus catarrh. The Paul-Bunnell test gave a reaction to a dilution of 1 in 80. This was repeated a fortnight later and the result was again positive, this time to a dilution of 1 in 10.

During his stay in hospital the patient felt well, but several transfusions were needed to keep his hæmoglobin at a satisfactory level. In view of the clinical picture, persistent lymphocytosis, and sternal marrow, the diagnosis of chronic lymphatic leuchæmia was made, the Paul-Bunnell reactions being regarded as not significant.

The patient was discharged on December 10, to be readmitted in a month.

Readmission to Hospital and Subsequent Progress.—The patient was readmitted to hospital on January 21, 1949. His tiredness had returned, but he had no other symptoms. He was pale, the size of the spleen and glands being unchanged.

A blood count performed by his doctor before his admission to hospital showed a hæmoglobin content of 55%, a white cell count of 16,000 per cubic millimetre, and 85% lymphocytes in the differential count. Urethane therapy was commenced on January 27. Since the hæmoglobin value and total white cell count were low, small doses were employed. For five days, a daily dose of 2·0 grammes was given, followed by 1·0 gramme daily.

By March 2 it was apparent that the treatment had been ineffective. The patient had had several attacks of pain under the left costal margin. The white cell count had risen to 56,000 per cubic millimetre, and the hæmoglobin value had fallen to 36%. A blood transfusion of one litre was given, and the urethane dosage was increased to 3·0 grammes a day. On the following day the patient developed a febrile reaction with pain and swelling of the spleen.

This soon abated, but within three days the patient began to feel nauseated and drowsy. (See Figure III.)

By March 14 the spleen was four inches below the costal margin. The palpable glands in the neck, the axillæ, and the groins had also increased in size.

On March 16 small petechiæ had appeared on both forearms. The Hess test for capillary fragility gave a positive result. Half a litre of blood was given on March 17, and one litre on March 23. The platelet count following the first transfusion was 40,000 per cubic millimetre, and following the second transfusion was 80,000 per cubic millimetre.

Sternal puncture was performed on March 24. The marrow was found to be very extensively infiltrated by lymphocytic cells, a fair proportion being immature, few megakaryocytes or other normal marrow elements being seen. (See Figure IV.) In view of the deterioration in the patient's condition, the enlargement of the spleen and glands, the persistence of large numbers of abnormal cells in the bone marrow, and the development of thrombocytopenia, it was decided to suspend the urethane administration and to refer the patient for deep X-ray therapy.

After the patient had been referred to the deep X-ray department several small treatments were given. On the morning of April 11 he developed a headache and later became drowsy and finally comatose. He died on the evening of that day. At autopsy a large cerebellar hæmorrhage was found. Smaller hæmorrhages were present on the surface of the cerebral hemispheres, the lungs and the heart. The spleen was greatly enlarged. Marked infiltration by lymphoid cells was noticed in the spleen and liver.

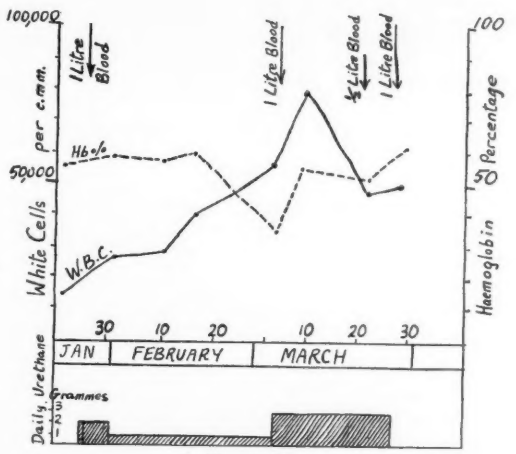

FIGURE III.

Case III. Almost complete failure at depression of leucocytes by urethane.

Discussion.

No favourable results occurred from urethane in any of our cases. In Case I considerable improvement occurred in the white cell count during treatment, but no clinical improvement occurred. This represents the spurious improvement described by Creskoff, in which hæmatological remission occurred together with clinical deterioration. In Case II no hæmatological improvement occurred, and the only clinical result obtained was slight diminution in size of the spleen. In Case III the white cell count steadily rose and the disease progressed unchecked by urethane.

In all three cases toxic effects were marked. Nausea and vomiting were extreme in the first two cases, in which the urethane accentuated the tendency to nausea produced by a large spleen and by the disease in its terminal stages. In Case III the patient was also nauseated and was drowsy. Although the nausea was not associated with the toxæmia of irradiation sickness, it was a great hindrance to the management of the patients. There was no clinical evidence of marrow aplasia in our cases. The thrombocytopenia in Case III was attributed to marrow replacement by lymphocytes rather than to toxic depression by urethane.

In both Cases II and III the bone marrow showed great numbers of abnormal cells, confirming our clinical impression of the inefficacy of urethane in their treatment. In Case III the marrow findings finally led to our abandonment of the treatment.

The suitability of such cases for urethane is open to question. In Cases I and II the patients were in the terminal stages of myeloid leuchæmia and were resistant to deep X-ray therapy when admitted to hospital. It was felt that, in spite of the advanced stage of the disease and the low hæmoglobin value, urethane was worthy of trial. In Case III, an early case of lymphatic leuchæmia, we were more hopeful of beneficial results.

In Case III the initially low leucocyte count provided a problem. It seemed wise, in our inexperience of urethane and its effects, to commence with small doses, which later proved ineffective. We feel in retrospect that if urethane is to be used at all it would be more effective and quite safe to use larger doses, such as 3·0 grammes a day.

In conclusion, we feel that urethane has little place, if any, in the treatment of terminal cases of leuchæmia. Its nauseating action gravely interferes with the nutrition of the patient, who is usually in poor appetite and often emaciated. We feel that it would be far better in such cases to try, by giving blood transfusions frequently and by administering protein hydrolysates by mouth, to improve the patient's condition sufficiently to allow a course of deep X-ray therapy.

Summary.

1. Two patients suffering from chronic myeloid leuchæmia and one suffering from chronic lymphatic leuchæmia were treated with urethane.

2. No benefit occurred from urethane in any of our cases.

3. The value of urethane in terminal cases of chronic myeloid leuchæmia is questioned.

Acknowledgements.

I am greatly indebted to Dr. A. J. Collins and to Dr. W. Bye for permission to report the cases, to Dr. Edgar Thomson for hæmatological advice, to Dr. G. F. S. Davies for permission to use the autopsy reports, and to Dr. J. P. O'Brien, of Prince Henry Hospital, for the photomicrograph.

References.

Creskoff, A. J., Fitz-Hugh, T., and Frost, J. W. (1948), "Urethane Therapy in Leukemia", *Blood*, Volume III, page 896.

Haddow, A., and Sexton, W. A. (1946), "Influence of Carbamic Esters (Urethane) on Experimental Animal Tumours", *Nature*, Volume CLVII, page 500.

Osgood, Edwin E. (1948), "Differential Diagnosis and Treatment of the Leukemias", *Northwest Medicine*, Volume XLVII, pages 181 and 257.

Paterson, E., Haddow, A., Thomas, I. A., and Watkinson, J. M. (1946), "Leuchæmia Treated with Urethane", *The Lancet*, Volume CCL, page 677.

Piney, A. (1947), *The Lancet*, Volume CCLIII, page 774.

Watkins, C. H., Cooper, T., and Giffin, H. Z. (1948), "The Use of Urethane in the Treatment of Leukemia", *Blood*, Volume III, page 892.

OTOGENIC BRAIN ABSCESS.[1]

By VOLNEY BULTEAU,

Sydney.

TEN years ago it could be said that the prognosis for brain abscess was no better than it was in McEwen's hands fifty years ago; indeed in some series it was worse. And this despite the fact that during those intervening forty years advances in neurology had made possible not only early diagnosis, but also exact localization. In addition surgical techniques had improved. What then was the stumbling block?

During the past ten years we have come a little closer to the answer to this question. This is epitomized by an

[1] Read at a meeting of the New South Wales Branch of the British Medical Association on April 28, 1949.

analysis of the cases at the Royal Prince Alfred Hospital during those ten years. The total number of cerebral abscesses was 58, of which 34 were otogenic. Of the 34 patients with otogenic cerebral abscesses, 13 were in adolescence and 21 in middle age.

These figures illustrate the approximate incidence of brain abscess at a hospital, such as the Royal Prince Alfred, where there are 36 beds for patients with ear, nose and throat conditions. That is to say, one can expect about six brain abscesses per year, of which about three or four will be otogenic. This number does not seem to have been appreciably changed by the introduction of penicillin in 1944, although, as may be seen later, the prognosis has been materially improved by it.

The figures for the age incidence of otogenic abscesses show two peaks: one in adolescence, the other in middle age. Outside of these, cases are very few. At first sight it is tempting to attribute the abscesses in adolescence to complications of acute or subacute middle ear infections and those in middle age to complications of chronic infections. This is not borne out, however, by an analysis of the histories. By far the greater proportion in this series, in both adolescence and middle age, followed chronic middle-ear disease of many years' duration.

The figures for mortality (Table I) show the improved prognosis since the advent of penicillin in 1944. This was to be expected. However, it was not altogether anticipated that the survivors would come entirely from the adolescent group. Their ages were 19, 15, 17, 17, 11 and 15 years respectively. Only one middle-aged patient survived, and he was the sole survivor in the pre-1944 era, but he represents one of the deaths in the post-1944 era, for he was readmitted about eighteen months later.

TABLE I.
Results from Otogenic Cerebral Abscess.

Result.	Number of Patients.	
	Before 1944.	After 1944.
Died	19	8
Survived	1	6
Total	20	14

Naturally an exhaustive exposition on brain abscess is not possible in the short time available; however, for your consideration this evening I should like to present some aspects of this grave malady. Since this is a general meeting of the Association the aspects for consideration will be those likely to be of interest and importance to men in other branches of practice, as well as those likely to concern the otologist and neurosurgeon.

In considering otogenic brain abscess one must first evaluate the types of middle ear disease which lead to it. With acute *otitis media* the likelihood of the occurrence of an abscess is minimal. Meningitis is the more likely complication of an acute infection which, by virtue of its virulence, carries a threat of intracranial spread. Rather is it the subacute infection, the *otitis media* which has been present for two, three or more weeks, which may lead to an abscess. The cases with persistently red bulging drumheads or nipple-shaped perforations and the cases due to the pneumococcus Type III are especially treacherous, particularly when, in the latter instance, apparent cure of the otitis has obscured its role as a causal factor. These cases are not as common as the cases due to chronic middle ear disease. With them the occurrence of an acute exacerbation, the presence of cholesteatoma in the epitympanic recess and a persistent offensive discharge are vitally important features. It has already been seen in the figures quoted how many of these abscesses have followed chronic middle ear suppuration—usually and unfortunately neglected for many years.

When an adult with long-standing chronic otorrhœa (associated with granulations, polypi or cholesteatoma) long neglected, attends again for treatment, it is prudent to enquire *why* the patient attends *now*. It is possibly because there has been some subtle difference of which the patient has now become aware—the harbingers of the impending intracranial complication. (Asherson).

For example, a man consulted me after flying to Sydney from Western Australia. He came because of a pain in the left side of his neck and increase in the amount of discharge from the left ear over and above that which had been present and not treated for fifteen years. He looked most unhappy. On examination of the patient an aural polypus and offensive discharge were found. He was Yugoslavian and difficult to interrogate and assess. Admission to hospital was arranged, but while he was waiting to go in there were further developments which I shall refer to later.

Sometimes the abscess may follow mastoidectomy, usually the cortical operation in which some infected cells are allowed to remain, or the attic may be imperfectly drained; it is exceptional for it to follow the radical operation.

These, then, are the types with abscess-forming propensities. If they are present any intracranial complication must be considered as an abscess until proved otherwise. Let us now follow the progress of the infection as it takes its various paths to the brain.

The Pathways of Infection.

It is possible for the infection to progress by contiguity and by continuity. If by contiguity, the infection follows the course so well shown in Turner and Reynolds's diagram (Figure I), that is, through the whole thickness of the

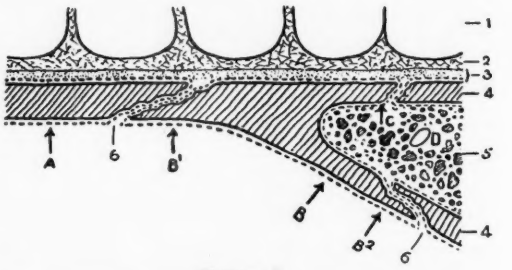

FIGURE I.

Diagrammatic representation of the cranial wall: 1, brain; 2, leptomeninges; 3, *dura mater*; 4, compact bone; 5, red bone marrow; 6, Haversian canal. (After A. L. Turner and F. E. Reynolds; from Swinburne, 1948.)

bone as at A or in diploic bone containing red marrow as at B, the diploë itself becoming infected before being eroded through at C. The sequence of events consists of inflammatory erosion of the bone, pachymeningitis, followed by the extradural abscess and finally a cortical abscess. It is this type which has a true stalk and therefore lends itself well to exposure through a mastoidectomy approach.

Continuity is the other possible mode of progress. In the course of the inflammatory erosion of the bone a Haversian canal may be laid open and the organisms brought into contact with the blood vessels. Infection passes along the blood vessels and through and beyond the dura. So it may be seen that the dura may appear perfectly normal on inspection and yet an abscess still be present. If a dural fistula is present at all it indicates an intradural abscess or rupture of an abscess, neither of which represents a preliminary change. The progress along the blood vessels is mainly perivascular and also intravascular; veins are almost always responsible, arteries rarely. Weed's diagram (Figure II) illustrates the path commonly taken.

The result is the implantation of the infection in the white matter. The site of predilection seems to be in a relatively avascular zone of the subcortex. Starting first

as a thrombosed capillary surrounded by a cuff of white blood cells, a localized area of encephalitis is produced.

A brain abscess arising from thrombosis of the lateral sinus is metastatic in its mode of formation and is frequently accompanied by abscesses in other organs. These metastatic brain abscesses do not obey Koerner's rule about adjacency, but otherwise they are no different from other brain abscesses.

Perineural extension may occur along the seventh and eighth cranial nerves. From the labyrinth infection may spread through the aqueduct of the cochlea or the aqueduct of the vestibule.

Expansion takes place at the expense of the white matter, the grey matter offering considerable resistance. As the infection progresses the contents come to consist of pus of varying consistency depending on the bacteria involved. The infection is usually a mixed one. The greater proportion of organisms are Gram-positive cocci and are

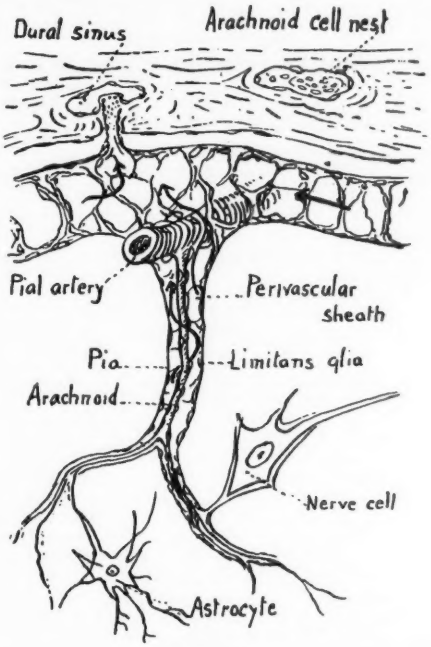

FIGURE II.

Diagram to show perivascular sheath and cerebro-spinal fluid circulation. (After Weed; from Swinburne, 1948.)

penicillin-sensitive. The walls of acute abscesses consist of necrotic tissue and behave like a phlegmon; those of chronic abscesses contain connective tissue and behave like an intracranial tumour. Estimates of the time taken to form a firm capsule vary from authority to authority; from two up to fourteen weeks have been reported. The consensus of opinion favours three or four weeks.

In recapitulating the important features about the spread one may say: the perivascular is the route most commonly taken; the intravascular is the most likely in lateral sinus thrombosis.

A localized area of encephalitis is produced in the white matter—not the cortex. Its subsequent behaviour depends on the well-known equation of virulence of organism and resistance of host.

The organisms are mostly sensitive to penicillin.

Clinical Course.

An awareness of this background which I have just described is of essential value in the interpretation of the clinical manifestations of the abscess. A constant pattern is all too infrequent. However, four phases are traditionally attributed to all abscesses: initial, quiescent, manifest and terminal. The first is caused by the initial encephalitis. It is characterized by an acute fever of varying intensity; if mild it is frequently described as a bout of influenza (this is particularly noticeable on reading back through case histories), or if it is severe, meningitis or lateral sinus thrombosis may come to mind. Malaria may be confused with it.

For instance, the Yugoslavian whom I mentioned previously was admitted to a medical ward of the Repatriation Hospital and given antimalarial treatment for a few days. He was then found to have a brain abscess, from which he subsequently died.

This phase is sometimes difficult to interpret. It may be quite overshadowed by the acute exacerbation of the ear disease itself.

The quiescent second (or "take down") phase is most elusive. During it the capsule is in process of formation. Headache is the most helpful single feature; its presence in association with any middle ear disease cannot be dismissed lightly. Physical examination during this phase may reveal very little abnormal. It is not difficult to imagine how one may be deluded into thinking that the treatment of the initial phase has been successful. I venture to suggest that personality changes usually take place and can be recognized during this phase, although my confidence in this was temporarily shaken last year by a patient under my care.

This man had been admitted to hospital with a provisional diagnosis of meningitis and had responded well to chemotherapy and a radical mastoidectomy for his chronic middle ear suppuration. He had no complaints after the immediate post-operative period and on examination the central nervous system was normal. Yet he seemed to me to be morose and reticent, and this I seized on as being a recent personality change. In my eagerness to "highlight" this sole symptom I waited until his wife came to visit him. She laughed when I asked whether these were new features of her husband's personality and replied: "For the past ten years or more the only times he ever says anything to me are on Saturdays when he is listening to the races." However, I was still suspicious, but when an encephalogram was normal I began to wonder. The result of ventriculography a little later was suggestive of a subtentorial lesion. Before anything further could be done he fell out of bed and was found dead on the floor. At autopsy his was a cerebellar abscess.

I mention this history also to illustrate that symptoms may be insidiously absent after the initial phase, even though one may suspect the presence of an abscess.

This now brings me to the third or manifest phase; it is then that something is obviously taking place in the brain. Fits, pareses, or coma may occur. A feverish attack may cause confusion with the initial phase. Of course, the significance of these manifestations is more obvious if the patient has already been under treatment for an ear condition. It is the case of the patient who first presents himself to the practitioner in any of these three phases which may be difficult to interpret. Rarely does he see the phases succeed each other. The importance of questioning for the presence of any history of ear disease in disorders of the nervous system should need no emphasis.

Fourthly comes the terminal phase—respiratory paralysis or meningitis.

Symptoms and Signs.

Systemic changes are usually marked. There are generalized signs of a serious illness—an illness out of proportion to the slight fever. Moreover, it does not respond to general measures and is clearly something far more than a purely local infection. The severity is proportional to the acuteness of the abscess.

General brain symptoms are noteworthy: "slow cerebration, heavy comprehension and marked want of sustained attention". This is McEwen's classical description and it conveys a strikingly apt picture of the mental state. Headache, of course, is of outstanding importance. Bradycardia indicates an increase in intracranial pressure and consequently in the severity of the condition. Nausea and vomiting occur initially, but do not last for long. Papil-

lœdema is important, but its absence does not mean that an abscess is therefore absent. The blood picture by itself is not characteristic.

These systemic and general brain symptoms may be vitally significant because of "the fact that focal symptoms are relatively late in appearing and it is not therefore wise to wait for them. The thing to go by is in the general state of the patient". (Neumann.)

Once the presence of an abscess is suspected, complete neurological investigation must be carried out. Cairns goes so far as to say that it should take precedence over mastoidectomy, since it will reveal more about what is happening inside the dura than can be seen from looking at a small portion of dura exposed in the region of the mastoid. It is now that collaboration between the otologist and neurosurgeon is all-important.

Examination of the cerebro-spinal fluid yields variable results. The pressure is usually increased. Cells are usually increased in number but rarely exceed 100, lymphocytes predominating. Protein is commonly increased in amount. The organism is frequently not demonstrable in the cerebro-spinal fluid. The amounts of chloride and sugar are said to be not diminished. (It has been noted that extremely low chloride values have been associated with a fatal outcome; for example, the man who died from the cerebellar abscess had a figure of about 650 milligrammes *per centum* on several occasions.) So it may be seen that the cerebro-spinal fluid examination by itself will not make the diagnosis. But considered in relation to the patient's general condition we are provided with a most useful diagnostic feature—the *syndrome de discordance*, in which the cerebro-spinal fluid findings improve, yet the patient's condition deteriorates.

It is sound practice to follow Sir Hugh Cairns's advice to arrange all clinical data on a large chart so that any day-to-day variation may be readily noted and its possible significance the more easily interpreted.

The general clinical features must be considered in conjunction with any local symptoms present. These will vary with the site of the abscess. Since most otogenic abscesses are adjacent, they will be either in the temporo-sphenoidal lobe or in the cerebellum.

In temporal lobe abscesses the local symptoms comprise disorders of speech and defects in the visual fields. The aphasia is usually nominal and the visual defect is commonly in the upper part of the field. Local brain symptoms due to pressure are varied and sometimes numerous; pressure on the contralateral hemisphere may produce false localizing signs.

In cerebellar abscess the local symptoms may consist of incoordination (finger-nose test), nystagmus, hypotonia and neck rigidity. If lateral sinus thrombosis is also present its symptoms tend to overshadow those of the abscess. It must be remembered that about two-thirds of cerebellar abscesses occur in connexion with disease of the labyrinth (and it is the latent type of labyrinthitis which causes abscesses rather than the manifest, the usual complication of which is meningitis). Therefore symptoms such as occipital headache, vomiting, vertigo and staggering are similar to labyrinthine symptoms. Consequently cerebellar abscess, cerebello-pontine angle tumours and labyrinthine disease are often confused.

The differential diagnosis not only of these but also of the many other features mentioned may be extremely difficult.

> The tendency to a mistake in diagnosis is increased by the fact that symptoms are slight and may be transient while the progress is slow. At the same time the very transiency of the signs is almost diagnostic. (Atkinson.)

Masking by chemotherapy may cloud the issue.

Nowadays newer ancillary methods of investigation are in use. These Dr. Phillips will discuss, together with their place in facilitating the making of a diagnosis.

To conclude my observations, I would again emphasize the foundation stones of our knowledge and recognition of otogenic brain abscesses:

1. A vigilant appraisal of the types of middle ear infection which are likely to produce an abscess; particularly the subacute otitis which persists in spite of all measures or the chronic infection with evidence of bone necrosis.

2. The pathways of infection which may be by: (*a*) Blood vessels—either along the sheath of the vessel or in the lumen—leading to a deeply seated infection. (*b*) Contact spread—a direct extension to the surface of the brain.

3. The phases in the course of most abscesses and a correlation of the clinical features with them.

4. Evaluation of the clinical features, facilitated by careful history taking and thorough examination of the central nervous system. Localizing signs are relatively late in their appearance. Hence the importance of systemic and general brain symptoms.

5. Danger signals in middle ear disease—headache and mental changes.

The prognosis, as you have seen, has improved during the past ten years. It behoves us then to be ever on the alert so that these abscesses will be recognized and the patient afforded the benefits which recent advances have contributed.

Acknowledgements.

Figures I and II are reproduced from a paper on "The Surgical Pathology of Brain Abscess" by George Swinburne, published in THE MEDICAL JOURNAL OF AUSTRALIA on August 14, 1948.

Reference.

Swinburne, George (1948), "The Surgical Pathology of Brain Abscess", THE MEDICAL JOURNAL OF AUSTRALIA, Volume II, page 169.

OTOGENIC ABSCESS.[1]

By GILBERT PHILLIPS,
Sydney.

AT the outset one may emphasize that otogenic cerebral abscess is a relatively rare condition. The published records of the neurosurgical unit at Oxford which review a total series of 3500 neurosurgical cases among patients admitted between 1940 and 1945 include only fifty cases of cerebral abscess due to all causes. The local incidence has been found to be about six cases of cerebral abscess *per annum* at the Royal Prince Alfred Hospital. As otogenic abscesses comprise somewhat less than 50% of the total, it becomes clear that, while abscess from this cause may be often suspected, it is seen quite infrequently.

The approach to the neurosurgeon in the review of suspected cerebral abscess of otogenic origin is made broadly under two conditions, namely, to exclude abscess in the presence of an acute or subacute infection of the mastoid cells or middle ear with or without meningitis, and to determine the cause of cerebral compression in a patient with a long-standing otorrhœa. These two groups represent the peaks in the age incidence of otogenic abscess, the first group represented mainly by adolescents, the latter by adults in or approaching middle age. The prognosis in the first group is considerably better than in the second, as the urgency of the condition demands early review, while in the latter the cerebral abscess represents a final stage in a long-continuing infection, and in these cases the abscess may be very large and may have provoked extensive cerebral œdema leading gradually to cerebral intoxication and compression. From the practical point of view, the management of these two types of case may be considered briefly under the heading of diagnosis and treatment.

In the first case, the patient with an acute infection of the mastoid cells or middle ear may present with signs of meningitis, of cerebral compression or of focal neural disturbance. Intracranial abscess becomes the provisional diagnosis until it is excluded. The matter is an urgent one and demands a good liaison between the otologist and the neurosurgeon. When the patient is first seen a complete neurological examination is indicated, with careful

[1] Read at a meeting of the New South Wales Branch of the British Medical Association on April 28, 1949.

checking for papillœdema, aphasia, Hutchinson pupil and pyramidal defects. These patients may not be good witnesses, but in view of the high incidence of otogenic abscess in the temporal lobe, some attempt should always be made to examine the visual fields even by confrontation. An electroencephalogram (Figure I) is always indicated, since in the presence of abscess this test would invariably reveal a slow wave dysrhythmia of delta frequency with phase reversals in the leads traversing the abscess. The cerebro-spinal fluid examination is important. Considerable increase in the protein content may be expected in 90% of cases, and the characteristic cell change is a pleocytosis, with five to fifty cells per cubic millimetre, a considerable proportion of which may be neutrophile cells. It should be remembered that the finding of even one neutrophile cell in the cerebro-spinal fluid is abnormal. If the intracranial pressure is high a minimal amount of cerebro-spinal fluid should be withdrawn for examination.

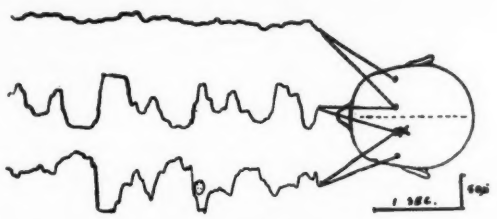

FIGURE I.

At this stage a decision may usually be made as to the likelihood of cerebral abscess, and in my opinion the next step requires a combined operation by the otologist and neurosurgeon. Adequate chemotherapy with penicillin and sulphadiazine should be instituted at an early stage, and in the operating theatre the otologist should drain the focus of infection. At the same procedure the neurosurgeon should make a burr hole over the site of the suspected abscess, open the dura and pass a brain needle into the hemisphere. If the abscess is not encountered the needle should be passed further into the ventricle, a ventriculogram prepared and abscess either definitely excluded or localized. If the abscess is encountered by the needle, pus is aspirated and one millilitre of penicillin solution containing 10,000 units per millilitre injected for every ten millilitres of pus aspirated. One or two millilitres of "Thorotrast" are then injected and the needle is removed. The course of events in the abscess cavity may now be studied precisely by radiographic examination (Figure II), and as a result a decision may be made from time to time to repeat aspiration and penicillin instillation. Cultures should be prepared from the first specimen of pus aspirated and the causal organism identified. Serial radiographic examinations reveal, at first, variations from day to day in the size of the abscess, but finally the abscess wall will be seen to become crenated and will collapse as the surrounding cerebral œdema recedes. When all signs of activity have passed, a formal operation for the removal of the abscess wall *in toto* should be carried out. Such an abscess wall is shown in Figure III. The close liaison in the early stages avoids the delays which may be so dangerous if one surgeon or other decides that his end of the problem should have the number one priority.

In the second group of cases the patients are usually referred directly to the neurosurgeon with focal or general signs of cerebral disturbance. The long-standing otorrhœa must never be disregarded as incidental, and demands the exclusion of chronic abscess as the cause of the illness. The problem here is usually the differential diagnosis of cerebral compression and may present considerable difficulty in a stuporose or aphasic subject. Again the four diagnostic steps suggested for the first group of cases should be followed, namely, full neurological examination, electroencephalography, cerebro-spinal fluid pressure estimation, protein and cell content determination, and finally burr-hole exploration on the suspected side with needling of the brain and ultimate ventriculography if the lesion is not encountered. There is little risk in air studies by ventriculography in these cases, provided the surgeon is ready to proceed immediately the abscess or other cause of compression is localized.

Finally one may observe that this condition, previously so lethal, may now be attacked with confidence in the knowledge that four out of five patients will recover with adequate management. This happy result stems from a combination of techniques, including the use of penicillin, abscess aspiration introduced by Dandy to ensure minimal disturbance within the skull, visualization of the abscess where indicated by air studies, and radiographic follow-up of the abscess after aspiration by the method using "Thorotrast" described by Kahn.

SOME OBSERVATIONS ON BIOPSY STUDIES IN DISEASES OF THE GALL-BLADDER AND OBSTRUCTIVE JAUNDICE.[1]

By J. W. PERRY,
Pathologist, Children's Hospital, Melbourne.

OBSTRUCTIVE JAUNDICE due to gall-stones or carcinoma of the pancreas commonly presents features both in the clinical history and physical examination which indicate the correct diagnosis. These features in addition to radiological evidence are sufficient in most cases to indicate laparotomy.

The surgeon, however, is sometimes left in a state of uncertainty and seeks biochemical tests, such as the usual tests of the urine for bile components, which may either establish the presence of subclinical jaundice or merely confirm an observation he has already made at the bedside.

The absence of bile pigment from the fæces or the presence of clay-coloured stools is suggestive of biliary obstruction, but it must be remembered that clay-coloured stools occur in parenchymatous jaundice, so that a more precise test may be required, such as the quantitative estimation of fæcal urobilinogen content, a persistently low output being highly suggestive of obstruction. In neoplastic obstruction the fæcal urobilinogen is usually minimal whilst urinary urobilinogen is absent. Obstruction due to stones produces a similar picture, but the levels usually fluctuate.

Both a highly elevated serum alkaline phosphatase and serum bilirubin content and a negative result from Hangar's test (cephalin flocculation) are of value in establishing the identity of obstructive jaundice, and these may be of great value in distinguishing some of the non-surgical types of jaundice, which sometimes mimic with distressing accuracy those conditions for which surgical intervention is essential.

If further help is needed, as in fact it may be, to decide between obstructive jaundice and an atypical form of infectious hepatitis, a specimen of liver obtained by the relatively simple technique of aspiration biopsy is often capable of dispelling any doubt that exists.

Before describing the changes in biopsy specimens typical of obstructive jaundice I should like to give a brief account of the liver changes in gall-bladder disease and obstructive jaundice.

Although present-day opinion holds that inflammation of the gall-bladder is due to an attack upon the gall-bladder itself by an irritant, either bacterial or chemical or both, this has not always been so.

In times when typhoid fever was a more prevalent disease and it was realized that in carrier states the presence of typhoid bacilli in the gall-bladder bile was due to excretion of the bacteria by the liver, or rather to their passage through this organ during the process of bile excretion, thought was turned to the possibility that other bacteria might gain entrance to the gall-bladder in

[1] Read at a meeting of the Section of Pathology, Australasian Medical Congress (British Medical Association), Sixth Session, Perth, August, 1948.

this way, and it was postulated by some that inflammation of the gall-bladder was secondary to inflammation in the liver. The work of Graham (1918), an American, on biopsy specimens of the liver removed at operation suggested that gall-bladder inflammation was always associated with diffuse hepatitis, but he was more inclined to emphasize the diffuseness of the involvement of the liver rather than to orientate the temporal relationship between liver and gall-bladder inflammation.

Opinion was influenced greatly by the experimental work of Wilkie (1928), who showed that in experimentally produced cholecystitis there was involvement of the liver, but only so long as the body of the gall-bladder was left in anatomical contact with the liver; if the organ was separated from the liver and a layer of great omentum interposed, no involvement of the liver occurred.

Peterman *et alii* (1921) observed that in dogs with experimentally produced cholecystitis the right lobe of the liver was mainly involved, and later observers, including Wilkie (1928), have shown that hepatitis associated with cholecystitis is confined to the right lobe and is in fact localized to the vicinity of the gall-bladder fossa, where its intensity bears a direct relationship to the intensity of that seen in the gall-bladder itself. Judd's (1921) views are pertinent in that he reminds us that the localized hepatitis in gall-bladder inflammation is seldom of clinical importance, in that, after removal of the gall-bladder, it is not progressive.

A study by Wood *et alii* (1948) of biopsy specimens taken from the right and left lobe of the liver at operation showed the hepatitis to be localized to the immediate vicinity of the gall-bladder.

The pooled result of these observations is that inflammation of the gall-bladder is primarily a disease of the gall-bladder, and liver involvement occurs because of its intimate association with the gall-bladder. The mode of spread of infection from the gall-bladder to the liver must be either by direct continuity, by blood-stream, or by lymphatics.

The importance of these observations lies in the conclusion that in inflammatory conditions of the gall-bladder, with or without stones, there is only a minimal hepatitis around the gall-bladder so long as there have been no episodes of obstruction to the common bile duct. This zonal hepatitis causes no impairment of liver function and heals after the gall-bladder has been removed. When obstruction to the common bile duct has been present, the pathological changes in the liver are quite different and are proportional in severity to the number and duration of obstructive attacks. Biopsy specimens, obtained both by the aspiration technique and at laparotomy, have defined a fairly clear-cut picture of the microscopic changes in the liver in obstructive jaundice. These changes have been emphasized by Wood *et alii* (1948), who remarked that the significant histological changes were found in those patients who either were jaundiced at the time of liver biopsy or had been jaundiced in the immediate past weeks. The changes are as follows:

1. Increase in the portal tract connective tissue with an openwork appearance suggestive of œdema. This connective tissue is the site of infiltration with inflammatory cells amongst which are polymorphonuclear leucocytes.

2. Changes in the bile-duct epithelium varying from swelling and loss of cellular outline to actual desquamation. In long-standing cases proliferation of bile-duct epithelium occurs.

3. Retention of bile pigment in the central lobular areas. Aggregation in the liver cells or bile canaliculi occurs always some distance from the portal tracts, although with long-standing obstruction bile pigment is diffusely scattered.

4. The histological demonstration of increased amounts of alkaline phosphatase.

These changes may be seen very early in a case of obstructive jaundice, indicating that soon after the obstructive episode has occurred there is commencing liver damage. This fact should be of interest to surgeons both because the changes take place early and because they are very highly suggestive of obstructive jaundice due to liver-cell damage.

The changes described above indicate that early in biliary obstruction the stage is set for biliary cirrhosis, a disease of the liver associated entirely with the aftermath of obstruction, and it can be clearly seen that recurrent episodes of obstruction in each case contribute materially towards the end result.

The presence of polymorphonuclear cells in the periportal connective tissue serves to remind how easily the progress towards biliary cirrhosis may be terminated by fatal suppurative cholangitis. The term "post-obstructive hepatitis" is more mindful of the events taking place in the liver than is biliary cirrhosis.

Before we leave the subject of biopsy study in relation to diseases of the gall-bladder and obstructive jaundice, it can be said that the procedure is of value as an aid to the solution of the occasional problem of the jaundiced patient for whom surgical intervention is of questionable necessity. Further, it has given us more precise information concerning the pathogenesis of post-obstructive liver disease.

Finally, a new note may be struck, for in the discussion of this relatively new technique it is important to remember that the field in which it has been most exploited is that of dietary liver disease. It is established that malnutrition contributes significantly towards human liver disease, and it behoves us to recognize that such factors may have played a part where they are least suspected. Attention has been drawn to the retarded healing of abdominal wounds in patients who have had long-continued dietetic treatment for peptic ulcer, and this retardation is directly related to vitamin *C* deficiency in the diet.

Attention may well be drawn to the patient with gall-bladder disease who unexpectedly has a stormy post-operative convalescence and to the relationship of coexisting liver disease of dietary origin as an explanation.

The following case report, which has appeared in a recent publication by Wood *et alii* (1948), illustrates this possibility.

Case Report.

A.D., a male, aged fifty-three years, had had several attacks of biliary colic in the past fourteen years. Four days before admission to hospital he suffered another attack of biliary colic and on this occasion became jaundiced. On his admission his temperature was normal, he was jaundiced, with tenderness and rigidity in the right subcostal region, and the liver was just palpable; biochemical tests revealed an elevated serum bilirubin content (16 units) and serum alkaline phosphatase content (30 units), and a negative result from Hangar's test (cephalin flocculation). Aspiration biopsy performed ten days after the onset of jaundice revealed a few polymorphonuclear cells in the connective tissue of the small portal tracts and in addition fat accumulation in liver cells (Figure I).

Three days later cholecystectomy was performed and stones were removed from the common bile duct. Another biopsy specimen of the liver obtained at operation contained similar changes to those seen in the aspiration biopsy specimen. Fat accumulation in liver cells was still obvious and alkaline phosphatase was histologically demonstrated in the second specimen in increased quantity.

His post-operative course was unsatisfactory in that he complained of severe depression and was reluctant to take food, and on the fourth day he suffered a collapse with rapid pulse rate and lowered blood pressure. An alkali reserve of 32% confirmed the clinical suspicion of acidosis, and intravenous therapy with glucose saline followed by protein hydrolysate was administered with good result, culminating over the next few days in complete recovery.

Comment.

Although it is conjectural that impaired liver efficiency contributed to the patient's unsatisfactory post-operative course, it is more than likely that its contribution was significant.

It may be that a period of careful dieting followed, if indicated, by a régime of feeding on a diet of high protein content is highly desirable and is perhaps a life-saving measure for patients about to undergo a major surgical procedure.

ILLUSTRATIONS TO THE ARTICLE BY DR. J. W. PERRY.

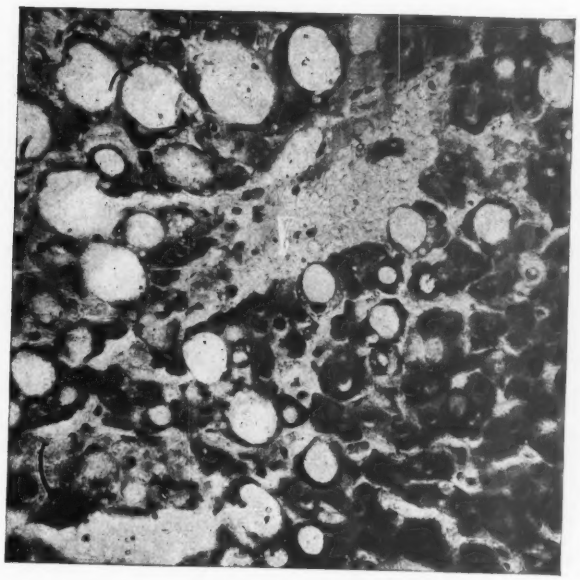

FIGURE I.

Specimen of liver obtained by aspiration biopsy from a patient with obstructive jaundice due to gall-stones. Section shows moderate accumulation of fat in the form of large vacuoles in liver cells. Hæmatoxylin and eosin × 450.

ILLUSTRATIONS TO THE ARTICLE BY DR. S. BENEDEK AND DR. V. J. McGOVERN.

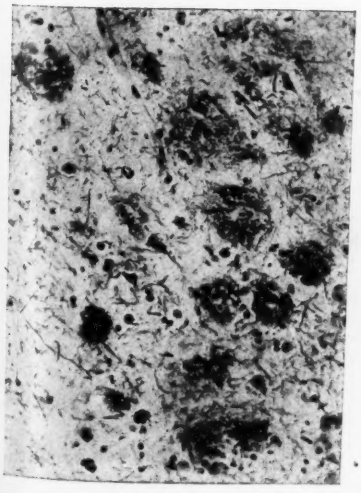

FIGURE I.

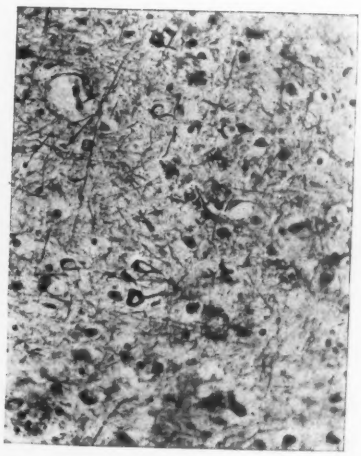

FIGURE II.

FIGURE III.

ILLUSTRATIONS TO THE ARTICLE BY DR. H. W. GARLICK AND DR. R. MOTTERAM.

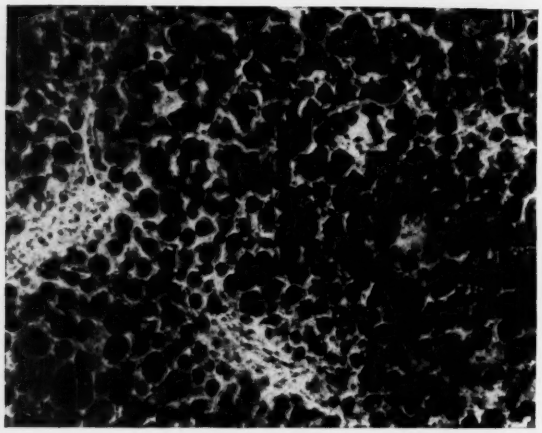

FIGURE II.

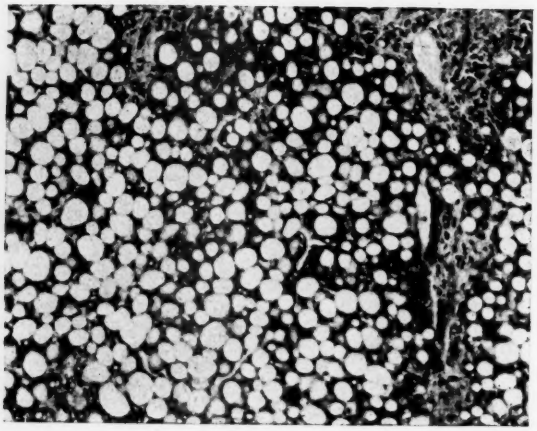

FIGURE III.

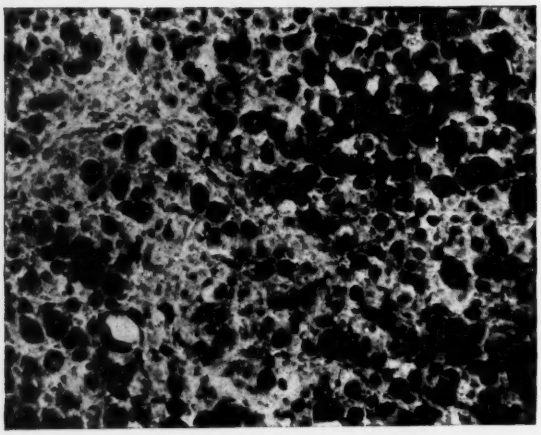

FIGURE IV.

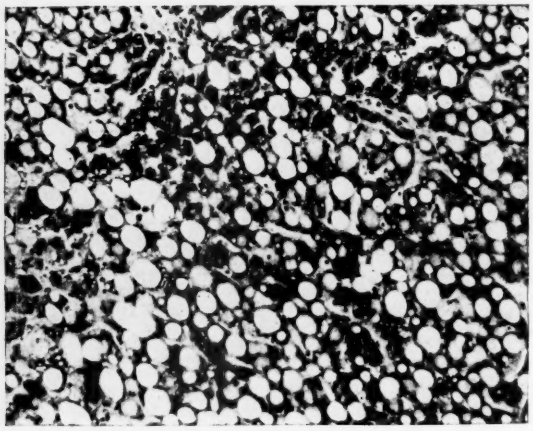

FIGURE V.

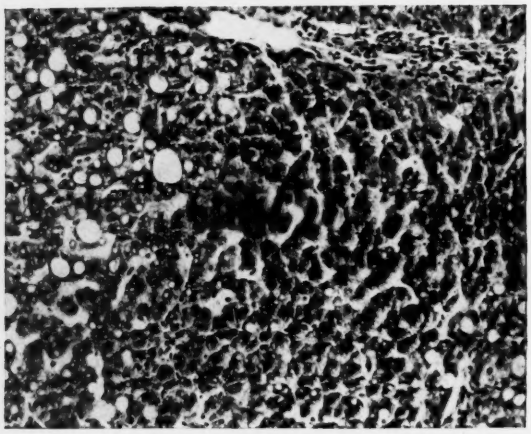

FIGURE VI.

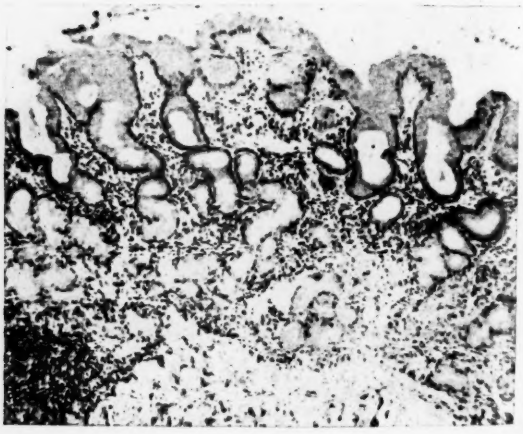

FIGURE VII.

Summary.

1. Biochemical tests combined with aspiration biopsy of the liver are of value in avoiding unnecessary laparotomy in cases of jaundice.

2. Obstructive jaundice is associated with histological changes in the liver which are quite characteristic, and such changes occur soon after obstruction occurs.

3. Biliary cirrhosis is a disease secondary to bile-duct obstruction, and the stage set for its development has been observed in biopsy studies of the liver in patients whose jaundice is of short duration.

4. A case is reported in which aspiration biopsy showed changes typical of obstructive jaundice and at the same time fat accumulation of moderate degree in the liver. It is suggested that this accumulation is probably due to malnutrition and that it indicated a degree of impairment of liver function sufficient to explain the unexpected post-operative collapse.

Acknowledgements.

My thanks are due to Dr. Ian Wood, head of the clinical research unit, Walter and Eliza Hall Institute, Royal Melbourne Hospital, for his advice and guidance, and to the pathology department of the University of Melbourne for preparing the photomicrograph.

References.

Graham, E. A. (1918), "Hepatitis: A Constant Accompaniment of Cholecystitis", *Surgery, Gynecology and Obstetrics*, Volume XXVI, page 521.

Wilkie, A. L. (1928), "The Significance of Hepatitis in Relation to Cholecystitis", *The British Journal of Surgery*, Volume XVI, page 214.

Peterman, M. G., Priest, W. S., and Graham, E. A. (1921), "The Association of Hepatitis with Experimental Cholecystitis in the Human", *Archives of Surgery*, Volume II, page 92.

Judd, E. S. (1921), "Relation of the Liver and Pancreas to Infection of the Gall Bladder", *The Journal of the American Medical Association*, Volume LXXVII, page 197.

Wood, I. J., King, W. E., Parsons, P. J., Perry, J. W., Freeman, M., and Limbrick, L. (1948), "Some Aspects of Cholelithiasis and Obstructive Jaundice", THE MEDICAL JOURNAL OF AUSTRALIA, Volume I, page 701.

Reports of Cases.

A CASE OF ALZHEIMER'S DISEASE WITH AMYLOIDOSIS OF THE VESSELS OF THE CEREBRAL CORTEX.

By S. BENEDEK,
Callan Park Mental Hospital,
AND
V. J. McGOVERN,
Department of Pathology, University of Sydney, Sydney.

ALZHEIMER'S DEMENTIA (Alzheimer, 1907) is a condition in which a clinical syndrome is often associated with characteristic pathological changes. The case presented here has a clinical picture which may be said to be characteristic, and the lesions in the brain may also be said to be characteristic. The unusual feature of amyloid change in the cortical vessels is the reason for reporting this case.

Clinical Record.

L.P., a male patient, aged forty-nine years, was admitted to Broughton Hall Psychiatric Clinic on June 4, 1945. For the previous two years the patient had shown gradually progressive mental deterioration. His memory for details had gradually failed and his efficiency as a railway ticket-collector declined. He became so disorientated that he accused his wife of hiding the lavatory as he could not find it.

On his admission to hospital he was euphoric and disorientated, misnaming objects and failing at picture symbols. His memory and comprehension were poor and he confabulated and falsified readily. Clinical examination revealed increased deep reflexes but no other abnormality. His blood pressure was 138 millimetres of mercury, systolic, and 90 millimetres, diastolic. His condition deteriorated gradually, and on October 8, 1945, he was transferred to Callan Park Mental Hospital.

In November, 1945, a pneumoencephalogram prepared by Dr. W. Lister Reid revealed dilated lateral ventricles and diffuse cortical atrophy.

In 1946 the patient began to have convulsive seizures followed by a period of some hours in a comatose condition, during which time twitching of the limbs occurred. Faulty sphincter control and incoherence became prominent about this time.

In August, 1948, after having been bedridden for some months, demented, mute and incontinent, with contractures of the lower limbs, the patient eventually died from bronchopneumonia.

Post-Mortem Examination.

At autopsy the immediate cause of death was found to be bronchopneumonia. The various organs weighed from 10% to 25% below the average normal weight, but apart from the lungs and brain appeared normal in other respects to the naked eye.

The brain weighed 1170 grammes and diffuse cortical atrophy was present, more pronounced on the right side and especially in the occipital pole. The vessels of the circle of Willis appeared normal. On section the lateral ventricles were found to be dilated on both sides.

On microscopic examination the pia-arachnoid is seen to be greatly thickened and many of the smaller vessels in the cortical regions have a hyaline thickening of their walls which reacts with Congo red in the same manner as amyloid. This vascular change is confined to the cerebrum. An occasional vessel has lipoid material in the wall, but no obvious arteriosclerosis has been detected.

Throughout the cerebral cortex are numerous senile plaques, especially in the parieto-temporal and occipital regions. The typical neurofibrillar changes of Alzheimer's disease are also prominent in the cerebral cortex. Argyrophile fibrils which encircle the blood vessels are increased in number. In the vicinity of the plaques and vessels there are small groups of fibrillary astrocytes, which are more argyrophilic than those in the normal brain. However, there is little increase in glial cells generally, but rod-shaped microglial cells are fairly common.

Many of the small vessels in the grey matter exhibit amyloid change in the same way as do those in the meninges. The vessels in the white matter of the cerebral hemispheres appear normal.

All the changes described above are more pronounced on the right side than on the left.

In the subcortical zones of the brain no plaques, neurofibrillar changes or signs of amyloidosis are demonstrable.

Unfortunately no other autopsy material is available for histological examination, and the extent of the amyloidosis cannot therefore be determined.

Comment.

Although Kinnier Wilson (1940) describes amyloid and lipoid material in the centres of plaques, none was found in this case. No additional evidence as to the genesis of the plaques or neurofibrillary changes has been observed. Nor was any relationship found between the characteristic changes of Alzheimer's disease and the amyloidosis of the vessels, apart from their recurrence in the same part of the brain.

Acknowledgements.

Thanks are due to Dr. E. S. Morris, Inspector-General of Mental Hospitals, Department of Public Health, New South Wales, for permission to publish this case; to Mr. S. Woodward-Smith, who prepared the photomicrographs; and to Mr. Bruce Munro, who made the histological preparations.

References.

Alzheimer, A. (1907), *"Über eine eigenartige Erkrankung der Hirnrinde", Allgemeine Zeitschrift für Psychiatrie,* Volume LXIV, page 146.

Kinnier Wilson, S. A. (1940), "Neurology", Volume II, page 919.

Legends to Illustrations.

FIGURE I.—Occipital cortex. Senile plaques and a neuron showing the typical neurofibrillar changes are shown. (Roger's neurofibril stain; × 200.)

FIGURE II.—Occipital cortex. A group of neurons showing the typical neurofibrillary changes. (Roger's neurofibril stain; × 200.)

FIGURE III.—Meningeal vessels stained for amyloid. The arrow points to a small vessel which does not give the amyloid reaction. (Congo red with hæmatoxylin counterstain; × 200.)

A CASE OF NUTRITIONAL DISEASE OF THE LIVER TREATED WITH CHOLINE AND STUDIED BY SERIAL ASPIRATION BIOPSIES OF THE LIVER.

By H. W. GARLICK,[1] M.R.A.C.P., AND R. MOTTERAM,[2] M.B., B.S., B.Sc.,

From the Walter and Eliza Hall Institute of Medical Research and the Royal Melbourne Hospital, Melbourne.

IT is well known that in fatty livers without fibrosis, treatment can cause a return to normal (Chester Jones and Volwiller,[(1)] King and Perry[(2)]). The patient described in this communication suffered from an extremely fatty liver induced by chronic alcoholism and associated malnutrition. The progressive absorption of the fat following the administration of a diet of high protein content and added choline was observed by serial liver biopsy performed at fortnightly intervals for a period of ten weeks. At the end of this time the liver had returned to normal. Function was assessed by serial biochemical investigations.

Clinical Record.

E.W., a female, aged fifty-seven years, was admitted to the Royal Melbourne Hospital on May 17, 1948. She had suffered from an ulcer type of dyspepsia for twenty years and during this period had had several hæmatemeses. The diagnosis of "gastric ulcer unproven" had been made at the time of previous admissions. On the present occasion she complained of general malaise for five months with anorexia and vomiting after meals, particularly in the morning. For the previous two months she had noticed a sensation of "pins and needles" in her hands and feet and her gait had been unsteady.

It was impossible to obtain an accurate and reliable dietetic history from the patient. However, her daughter stated that she had been a heavy drinker of cheap wine for at least ten years but more so over the last twelve months. For some years her diet had been most inadequate and consisted chiefly of carbohydrate. The appearance of the patient and the almoner's report (based on visits to the patient's home after discharge from hospital) confirmed the fact that she was a chronic alcoholic.

On examination she appeared very ill. She was drowsy and had a coarse tremor of the hands and tongue. The temperature was not raised. The liver was palpable ten centimetres below the right costal margin, and the spleen was palpable one centimetre below the left costal margin. Peripheral neuritis was evidenced by the absence of deep reflexes, and there was glove and stocking anæsthesia with tenderness of the calf muscles.

Investigations.

Liver Function Tests.—The serum bilirubin content was two units (normal 0·2 to 1·0 unit); the result of the cephalin flocculation test was weakly positive; the total serum protein content was 5·3 grammes per 100 millilitres with a normal albumin:globulin ratio (1·5); hippuric acid excretion was impaired (1·3 grammes); the alkaline phosphatase content of serum was 11 units (normal 3 to 13 units); the prothrombin index was 97%.

Glucose Tolerance Test.—The fasting blood sugar was 145 milligrammes per 100 millilitres and after 50 grammes of glucose given orally it rose to 210 milligrammes and was still 194 milligrammes after two hours (see Figure I).

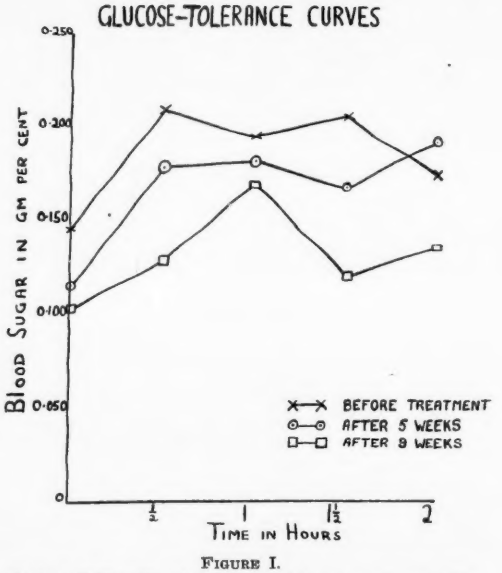

FIGURE I.

Patient E.W. Showing glucose tolerance curves after 50 grammes of glucose: (*a*) before treatment; (*b*) after five weeks; (*c*) after nine weeks' treatment with diet and choline to show a progressive return to normal. (Case of fatty liver resulting from chronic alcoholism and malnutrition.)

Fractional Test Meal.—Histamine-fast achlorhydria was revealed by examination of a fractional test meal.

Gastroscopy.—Atrophic gastritis was detected by means of the gastroscope.

Opaque Meal Report.—The œsophagus, stomach and duodenum appeared normal on X-ray examination after an opaque meal.

Gastric Biopsy.—Gastric biopsy was performed by the technique described by Wood *et alii.*[(3)] Examination of the section showed an atrophic gastritis (see Figure VII).

Aspiration Biopsy of the Liver.—Aspiration biopsy of the liver, performed by the technique of King and Perry,[(4)] showed the liver architecture to be normal. There was extensive fatty vacuolization of all the parenchymal cells (see Figure II) so that the cytoplasm was compressed to a thin rim at the periphery. This residual cytoplasm showed a good glycogen filling (see Figure III). It was notable that fibrous tissue increase was minimal and confined to the portal tracts.

Treatment.

It was considered that the fatty change in the liver should be reversible by means of a diet rich in lipotropic factors. The patient was given a diet of high vitamin content, which contained 3000 Calories a day, made up of 140 grammes of protein, 500 grammes of carbohydrate and 50 grammes of fat. The foods which are rich in the amino acid methionine were selected in this diet, namely, cheese, eggs, milk and meat. In addition the patient was given 12 grammes of choline chloride by mouth each day and intramuscular injections of vitamin B_1. This treat-

[1] Wyeth Fellow in Medicine.

[2] Aided by a grant from the National Health and Medical Research Council.

ment was continued for a period of ten weeks while the patient was in hospital, and during this time she abstained from alcohol.

Response to Treatment.

The clinical improvement was rapid. After two weeks the patient felt generally much better, she regained her appetite, the spleen became impalpable and the liver gradually diminished in size. After three weeks she was able to sit out of bed and, aided by diet, vitamins and physiotherapy, her peripheral neuritis showed gradual improvement. At the end of ten weeks she was clinically well and the liver was palpable three centimetres below the right costal margin. The serum bilirubin level had fallen to 0·2 unit, her serum failed to flocculate cephalin and her hippuric acid excretion had risen to 2·1 grammes. Glucose tolerance tests were repeated five weeks and again nine weeks after commencement of treatment. These tests showed a progressive return to normal (see Figure I).

Aspiration biopsy of the liver was performed at intervals of two weeks over a period of ten weeks. Examination of these sections showed a considerable diminution in the amount of fat in the liver after two weeks of treatment (see Figure VI), more especially from the cells of the peripheral portions of the lobules. Improvement was then more gradual. At the end of eight weeks only a few polygonal cells in the centrolobular areas showed fat globules (see Figure VI).

Discussion.

This seriously ill woman suffering from chronic alcoholism and malnutrition made a dramatic improvement when treated with diet and choline. Absence of lipotropic substances in her diet and alcoholic excess had induced a gross fatty accumulation in her liver. However, the original liver biopsy showed normal architecture with preservation of the liver cell cord arrangement. It is in these earlier cases of fatty liver with minimal fibrosis that one can expect a return to normal with lipotropic therapy. There is general agreement that the sample obtained by needle biopsy can be taken as typical of the trend in the whole liver, and therefore by serial biopsy we have an accurate histological measure of the value of lipotropic therapy. In the present case the fat content had diminished greatly in two weeks and had almost completely disappeared in two months. Clinical and functional improvement agreed closely with the appearance of the liver parenchyma at the various stages.

There appeared to be an interesting correlation between progress glucose tolerance curves and the increased glycogen storage consequent upon the removal of the fat globules from the parenchymal cells (see Figures V and VI). In view of the previous history of dyspepsia and gastric hæmorrhage it is significant to note that the gastric biopsy showed advanced atrophic gastritis.

Summary.

1. A patient suffering from fatty change in the liver caused by chronic alcoholism and malnutrition is described.

2. Treatment with a full diet and added choline combined with abstinence from alcohol caused dramatic improvement in the clinical condition of the patient.

3. With the use of needle biopsy the morphological improvement in the liver was observed at fortnightly intervals for a period of ten weeks.

4. Absorption of the fat was considerable after two weeks of treatment and was almost complete after two months.

5. Clinical improvement and improvement in liver function tests corresponded to the absorption of the fat.

6. There appeared to be a correlation between progress glucose tolerance curves and the increased glycogen storage consequent upon the removal of the fat globules from the parenchymal cells of the liver.

Acknowledgements.

We wish to acknowledge the help we received from Dr. Ian Wood and members of the Clinical Research Unit. The photomicrographs were prepared by Mr. H. Mathei of the University of Melbourne.

References.

(1) Chester Jones and W. Volwiler: "Therapeutic Considerations in Subacute and Chronic Hepatitis", *Medical Clinics of North America*, Boston Number, September, 1947, page 1059.

(2) W. E. King and J. W. Perry: "Liver Changes in Alcoholism Studied by Aspiration Biopsy of the Liver with Report of a Case", *Royal Melbourne Hospital Clinical Reports*, Volume XVIII, December, 1947, page 71.

(3) I. J. Wood, R. K. Doig, R. Motteram and A. Hughes: "Gastric Biopsy: A Report on Fifty-five Biopsies Using a New Flexible Gastric Biopsy Tube", *The Lancet*, Volume I, 1949, page 18.

(4) W. E. King and J. W. Perry: "Technique of Aspiration Biopsy of the Liver with Reference to Its Use in Diagnosis and Prognosis", THE MEDICAL JOURNAL OF AUSTRALIA, Volume I, 1948, page 697.

Legends to Illustrations.

FIGURE II.—Patient E.W. Aspiration liver biopsy before treatment. Fat stain showing the extreme degree of fatty accumulation in the parenchymal cells. (Case of fatty liver resulting from chronic alcoholism and malnutrition.) (Frozen section stained by Schariach R. × 125.)

FIGURE III.—Patient E.W. Aspiration liver biopsy before treatment. Best's carmine stain to show glycogen in the thin rim of cytoplasm surrounding the fatty vacuoles in the parenchymal cells. (Case of fatty liver resulting from chronic alcoholism and malnutrition.) (× 125.)

FIGURE IV.—Patient E.W. Aspiration liver biopsy after two weeks of treatment with diet and choline, showing a very considerable clearing of the fat, especially from the peripheral portions of the lobules. (Case of fatty liver resulting from chronic alcoholism and malnutrition.) (Frozen section stained with Schariach R.) (× 125.)

FIGURE V.—Patient E.W. Aspiration liver biopsy after two weeks of treatment with diet and choline. Best's carmine glycogen stain showing some absorption of fat and increased glycogen storage in parenchymal cells at the periphery of lobules. (Case of fatty liver resulting from chronic alcoholism and malnutrition.) (× 125.)

FIGURE VI.—Patient E.W. Aspiration liver biopsy after eight weeks of treatment with diet and choline stained for glycogen showing only a few scattered fat vacuoles. The majority of the parenchymal cells now have abundant cytoplasm with a normal glycogen content. (Case of fatty liver resulting from chronic alcoholism and malnutrition.) (× 125.)

FIGURE VII.—Patient E.W. Gastric biopsy from the mucosa of the body of the stomach showing complete atrophy of the acid and pepsin-secreting glands and replacement by mucus-secreting glands. (Case of fatty liver resulting from chronic alcoholism and malnutrition. There was a history of chronic dyspepsia and hæmatemesis, and examination of a test meal revealed histamine-fast achlorhydria.) (Mucicarmine stain. × 75.)

TWO UNUSUAL ABNORMALITIES OF MECKEL'S DIVERTICULUM.

By G. M. B. HALES,
Sydney.

MECKEL'S DIVERTICULUM is stated to be present in about 2% of persons, and at times is connected by a cord, representing the primitive vitelline duct, to the umbilicus. Rarely, this cord retains a lumen and a sinus is formed discharging intestinal contents at the umbilicus. Ladd (1947) records one such case in a series of 73 in which the diverticulum caused pathological conditions.

A search through the literature available has shown no record of cases similar to those reported here.

CASE I.—P.C., aged nine days, was admitted to the Royal Alexandra Hospital for Children on June 13, 1948, with a provisional diagnosis of biliary fistula. The history given was of a normal birth. On the fourth day clear fluid was noticed coming from the umbilicus, and by the seventh day the discharge was greenish in colour and sticky.

Physical examination revealed no abnormality except that at the umbilicus there was protruding a structure about one inch long and half an inch in diameter which appeared to be the base of the umbilical cord. At the apex of this mass was an opening through which yellow fluid was exuding, and through which a probe could be introduced for about half an inch.

A right paramedian incision was made and a Meckel's diverticulum was found passing through the umbilicus. This was clamped and cut and the end attached to the bowel was oversewn. The distal end was coagulated, the wound closed, and the protruding portion removed by diathermy excision.

In this case it would appear that the diverticulum at birth extended into the base of the umbilical cord, and when the latter was tied the apex was included in the ligature. When this sloughed off the diverticulum opened at the end of the cord stump.

CASE II.—H.I. was born on August 14, 1948. The birth was normal and no abnormality was noticed in the child for the first three weeks. Then a small, red area was seen in the umbilicus and considered to be granulation tissue.

On September 16 a mass about one inch long suddenly protruded from the umbilicus. This was covered with red hæmorrhagic mucous membrane and an aperture was present at its apex. A diagnosis of eversion of a Meckel's diverticulum was made and the child was admitted to hospital.

At operation a Meckel's diverticulum was found, about one and a half inches being intraabdominal and the same amount extraabdominal, with a diameter of half an inch. It was attached by its distal end to the umbilicus and had then telescoped through itself. The diverticulum was cut, the proximal end was oversewn and the distal portion was brought out through the umbilicus and removed by diathermy excision.

An additional abnormality present in this case was a cord-like band attached at its exremities to the root of the mesentery and the umbilicus and otherwise free. It was tied and divided and had no lumen.

Reference.

Ladd, W. E., and Gross, R. E. (1947), "Abdominal Surgery of Infancy and Childhood", page 73.

Reviews.

PAPERS ON PSYCHO-ANALYSIS.

DR. ERNEST JONES has published the fifth edition of his famous "Papers on Psycho-Analysis".[1] He states that this is positively the final edition. The reader will hope that this emphatic statement belongs to the psychopathology of everyday life and betokens an inner desire to write yet again.

Through the years Ernest Jones has become an institution among psychiatrists. By his scholarly and readable prose he has given the bases of psychological insight to many thousands. This volume lives up to the standard of its predecessors. Fourteen papers have been deleted and nine more recent papers included. The complete set includes eighty-nine.

More recent graduates who have not grown up with the intense psycho-analytic controversy which existed twenty years ago, may find it difficult to realize that the author was in the spearhead of the movement. His impartiality is in itself a triumph for the psycho-analytical outlook. He considers that our world of today is one influenced by political trends, which overstress the use of material environment to create happiness. As a psycho-analyst he stresses the greater importance of internal mental constitution of the individual, the unconscious processes partly dependent upon heredity and infantile experiences.

The volume commences with papers on Freud's psychology and the psychopathology of everyday life. Both should be read by every practitioner. The first outlines the dynamic approach, the latter gives the types of behaviour slips which betray the real individual. In medical practice, a gesture, a slip of the tongue or pen may be important clues to diagnosis and it may be added—to the doctor's own psychology. As an example may be quoted his case of a young American who had had a "certain experience in her childhood in company with a boy. I had every reason to believe that this was far from being an isolated one, and asked her whether it had occurred with anyone else. She said, 'Not any time that I can remember.' Noticing the wording of her answer and a certain expression on her face, I asked, 'What about the times that you can't remember?' She exclaimed, 'Oh, Shucks!', and in such a disconcerted tone that I was sure my surmise had been well founded. She then made the remark, 'Well, I really had forgotten the other times till this minute', the truth of which was probably only partial".

The chapter on "The Genesis of the Super-ego" was first published in 1947. The author points out that the Freudian views have been modified. Although the super-ego is heir to the Œdipus complex, it is born of fears of punishment and anxieties which occur as early as the first year of life. The author asks that an angry baby should not be allowed to "cry itself out", since "The dread of this total exhaustion of the libido" which "I have termed the fear of aphanasis . . . is in my opinion the important starting-point of the anxiety against which the super-ego, as well as other defences, is instituted".

The chapter on "Psychology and War Conditions" is an interesting historical account of the analyst's viewpoint in the Britain of 1944. The author pays tribute to barbitone and insulin treatment. In reference to the first great trial for the British people when the Germans were marching on France, he recalled the uplift which occurred after the actual surrender of France. "At a time when we had to realize that we stood alone against the invincible and ruthless tyrant a lady made the rather surprising remark to me: 'Thank goodness there are no longer any allies we have to praise'."

The second trial of the blitz was helped by the roar of the anti-aircraft defence which raised the morale. The third trial of strain and weariness is, alas, still being felt.

In discussing the solution to the war problem, Dr. Jones states that war is a reaction to intolerable anxieties and guilts. He asks that we cease to find scapegoats through class and racial hatred, but search for a sane psychological approach.

"The Concept of the Normal Mind" deals with a theme which has occurred to many a harassed doctor, who has wondered if any of his patients are sane. The answer is in the negative. "As we do not meet absolute perfection elsewhere in the universe, even in Newton's Laws of Motion, it would be astonishing ever to find it in such a wry locality as the mind of man." However, the reader need not be unduly dismayed. It is surprising how much can be concealed and achieved without recourse to the psychiatrist.

In addition to the above list of chapters, the book covers a wide field including psycho-analysis and instincts, love and morality, dreams and psychoneurotic symptoms, fear, guilt and hate, jealousy, criteria of success in treatment, anal-erotic character traits, early female sexuality *et cetera*. Space will not permit further discussion of this stimulating potpourri of psychological material. Enough has been written to indicate its worthiness to a place on the bookshelf.

[1] "Papers on Psycho-Analysis", by Ernest Jones, M.D., F.R.C.P. (London); Fifth Edition; 1948. London: Baillière, Tindall and Cox. 8½" × 5½", pp. 516. Price: 31s. 6d.

Books Received.

[The mention of a book in this column does not imply that no review will appear in a subsequent issue.]

"The Science and Art of Joint Manipulation", by James Menneil, M.A., M.D., B.C. (Cantab.); Second Edition; Volume I; 1949. London: J. and A. Churchill, Limited. 9½" × 7", pp. 236, with 299 illustrations. Price: 24s.

The first edition appeared in 1939.

"The National Health Service", by Charles Hill, M.D., and John Woodcock; 1949. London: Christopher Johnson Publishers, Limited. 7" × 4½", pp. 440. Price: 16s.

An explanation of how the scheme works.

"Manual of Medical Emergencies", by Stuart C. Cullen, M.D., and E. G. Bross, M.D.; 1949. Chicago: The Year Book Publishers, Incorporated. 7" × 4½", pp. 274, with 29 illustrations. Price: $3.75.

Designed to cover the acute emergency only.

"Advances in Internal Medicine", edited by William Dock, M.D., and I. Snapper, M.D.; Volume III; 1949. New York: Interscience Publishers, Incorporated. 9" × 6", pp. 498, with a few illustrations. Price: $8.50.

Contains ten chapters covering a wide range of subjects, the work of many contributors.

The Medical Journal of Australia

SATURDAY, SEPTEMBER 17, 1949.

All articles submitted for publication in this journal should be typed with double or treble spacing. Carbon copies should not be sent. Authors are requested to avoid the use of abbreviations and not to underline either words or phrases.

References to articles and books should be carefully checked. In a reference the following information should be given without abbreviation: surname of author, initials of author, year, full title of article, name of journal without abbreviation, volume, number of first page of the article. If a reference is made to an abstract of a paper, the name of the original journal, together with that of the journal in which the abstract has appeared, should be given with full date in each instance.

Authors who are not accustomed to preparing drawings or photographic prints for reproduction are invited to seek the advice of the Editor.

THE CYTOLOGICAL DIAGNOSIS OF MALIGNANT DISEASE.

DURING recent years a good deal of attention has been given to the diagnosis of malignant disease by the discovery of malignant cells in the secretions and fluids of the body. This has been due mainly to the work of G. N. Papanicolaou, who with H. F. Traut in 1943 published a monograph on the diagnosis of uterine cancer by the vaginal smear. Papanicolaou caused a reawakening of interest; he did not introduce a new method. This has been made quite clear by him and by others who in October, 1948, at Chicago took part in a symposium on the subject at the annual meeting of the American Society of Clinical Pathologists.[1] Lücke and Klebs in 1867 drew attention to the presence of tumour cells in exudates, and Quincke in 1882 described in exudates tumour cells that were aggregated in clumps; but it was after the introduction by Ehrlich of effective staining methods that smear diagnosis was made with greater certainty. Few, if any, reports have been published in Australia on the use of exfoliative cytology as a diagnostic method. Papers were read on the use of the vaginal smear in the diagnosis of cancer of the cervix at a meeting of the New South Wales Branch of the British Medical Association in July, 1948. The papers, however, were not submitted to this journal for publication and the discussion therefore did not see the light of day. The Chicago symposium of last October covered many aspects of the subject and should in the circumstances be brought to the notice of Australian practitioners.

The first paper on the examination of vaginal and uterine secretions in the diagnosis of uterine cancer was read by Papanicolaou. At an early stage he made a remark which needs special emphasis—that a point had not been reached at which vaginal smear examination could be regarded as a method of final diagnosis. He described four types of smear which were best suited to the method. He pointed out that the criteria used in the cytological diagnosis of cancer were based on structural modifications of the cancer cells and of their nuclei as well as on changes in their relationship and pattern when in groups and clusters. In the early stages of his work Papanicolaou's diagnostic objective had been limited to a decision whether malignant change was or was not present. He said that increased knowledge and experience were enabling him to recognize with greater confidence certain characteristic cell or smear types, which in some instances made possible an evaluation of the type of tumour as well. Some of the basic difficulties were mentioned in the unpublished New South Wales discussion by A. H. Tebbutt. He pointed out that in some cases one met with hyperplasia of the cervical epithelium or glands and with actual metaplastic changes in the cells, but not with malignant infiltration. He asked what those cells were to be called if they were seen in a vaginal smear. If they were met with in a biopsy they were not called cancer cells, but if they were seen in a vaginal smear the cytologist might well call them cancer cells. Tebbutt was in favour of the adoption of a conservative attitude, especially in regard to interpretation. Some of the figures quoted by Papanicolaou were striking. For example, in twenty positive cases among a group of 124 patients with symptoms, a diagnosis of malignant disease had been confirmed by biopsy; two of the cases had been reported by him to be "negative". In a second group of 777 patients, most of whom were asymptomatic, there were 11 positive cases confirmed by biopsy; in one of these 11 a "negative" report had been given.

Among the other papers presented at the symposium was one by Otto Saphir on cytological diagnosis of cancer from pleural and peritoneal fluids. He reported a high proportion of successful diagnoses—37 correct diagnoses in 45 cases in which the pleura or peritoneum was involved by carcinoma. He insisted that the outstanding characteristic of malignant tumour cells in individual smears was the large, sometimes irregular nucleus. The diagnosis of malignant disease in his preparations rested solely on the observation of the nucleus—its size, the presence of large nucleoli and the finding of obvious atypical mitoses. It is of interest that in one instance a diagnosis of carcinoma was made from a smear taken from peritoneal exudate and that at autopsy cirrhosis of the liver was found but no carcinoma. Among the diagnoses were two "false negatives". P. A. Herbut, on behalf of himself and E. M. Lubin, discussed the cytological diagnosis of carcinoma of the prostate. He found that a positive cytological diagnosis had its greatest value in cases which were clinically uncertain, but he insisted that a negative finding did not mean that the patient was free from cancer. In his opinion experience was most important, for some of his earlier findings which were equivocal would not, he thought, have been made in the later stages of his work. M. Appel and T. T. Bronk reported experimental work undertaken because they had some difficulty in finding a malignant tumour in a lung; this had been removed from a patient whose bronchial secretions from the lung in which the tumour was found contained malignant cells, though bronchoscopy yielded no evidence of a tumour. By experimental means they produced pulmonary carcinoma in rabbits. Exfoliated cells could be found in every instance at some time or other during the development of the tumour. In more than half the cases tumour cells could be found in the secretions before

[1] *The American Journal of Clinical Pathology*, April, 1949.

the tumour was grossly recognizable and at a stage at which neither X-ray examination nor bronchoscopy could have identified the growth. H. L. Richardson, W. C. Hunter, W. S. Conklin and A. B. Petersen described a method for the fixation of secretion removed from the bronchi by aspiration. Their report deals with 36 cases of pulmonary neoplasm. The important point about their findings is that bronchial secretions contained carcinoma cells in four cases in which tissue was unobtainable or in which biopsy yielded negative findings and that in no case were the aspirations "negative" when biopsy revealed neoplastic tissue. The last paper in the symposium was presented by H. L. Richardson, F. B. Queen and F. H. Bishop, who dealt with the cytological diagnosis of material aspirated from the stomach. This is a long paper, and it is neither possible nor necessary to attempt to cover the findings. With the exception of one, all the cancers were large and advanced and presumably a diagnosis could have been made by other methods than the examination of gastric washings. The one case, however, was particularly striking. In this instance a diagnosis was made on cytohistological evidence before X-ray examination or gastroscopy was performed. In the specimen removed at operation a small cancer one millimetre in diameter, invading the muscularis, was found in the margin of an ulcer. On the other hand a false-positive diagnosis of normal was made in 10% of cases.

The discussion was opened by William Boyd, whose authority as a pathologist need not be questioned. *Inter alia* he referred to carcinoma *in situ*. He thought that without doubt there was such a thing—it could not be otherwise, because cancer had to be *in situ* before it began to invade deeper tissues. The term was possibly greatly abused. But this is by the way. In regard to the value of the method Boyd pointed out, as we all know, that scientific discoveries which have been hailed at first as fresh triumphs over Nature lead to disillusionment when their limitations are realized. He added that this occurred only if there was a "tremendous ballyhoo" at the start. The function of the pathologist, he declared, was to be conservative in outlook and to impress clinicians with his conservatism. It was the clinician's job to impress on the public the true state of affairs. When they are dealing with their own patients it is simple for clinicians to explain that a search will be made for certain manifestations, that failure to find them will give no reliable guide and that success will be of assistance in the planning of treatment and no more. The method is not difficult—this has been emphasized by Tebbutt. It is experience that is needed, and this is quite clear from the Chicago symposium. Boyd stated that a manufacturer of laboratory equipment had advertised the sale of materials for the Papanicolaou test with slides of various types of cell; the only thing which the firm did not and could not sell was "the most important ingredient"—a competent pathologist. In the past discussions have taken place in this journal on "the worship of the test tube"; this is the same as worship of the laboratory test. This worship is all very well—in moderation. It should be worship (if worship it must be) of wise discrimination and not of wholehearted, exclusive devotion.

Current Comment.

NUTRITIONAL FACTORS IN ANTIBODY FORMATION.

IT is a truism that the capacity of the body to produce antibodies in response to a challenge by infective agents must depend to some extent on the existing state of its nutrition. In particular the level of protein in the body fluids and the intake of protein are concerned, with emphasis on the globulins, since it is believed that antibodies are modified globulins. Though the nature of the actual response to an antigen is still obscure, the necessity for the correct material for its successful performance by the body will be conceded. Michael G. Wohl, John G. Reinhold and S. Brandt Rose in a contribution to the study of antibody response from the clinical aspect base their work on previous work on animals.[1] Cannon and other investigators have shown that antibody production is lessened in experimental animals when the protein content of the blood is reduced. Others have proved the converse, that when the blood protein is brought up to the normal level antibody response is correspondingly enhanced. These results cannot be wholly applied to the human subject. For one thing, the protein depletion in the experimental animals was often very considerable before antibody production was substantially impaired. The present investigation was designed to assess antibody production in human subjects suffering from hypoproteinæmia, to test the effect of an increased intake of nitrogen on the formation of plasma protein and antibodies, and to compare the effectiveness of various hydrolysates and similar preparations in treatment. Patients were selected from hospital wards who had a serum albumin content of below 4·0 grammes per hundred millilitres; this measurement was preferred to total protein content because increased globulin might mask protein depletion by reason of infection or liver disease. These patients were divided into three groups. One received the standard hospital diet, with 80 grammes daily of lactalbumin hydrolysate, equivalent to 59 grammes of protein; another received the same standard and supplementary diet and in addition inoculation with typhoid vaccine; while a third group underwent the same immunization, but received the standard diet only. None of these patients were very ill. Two other groups were also studied, one receiving 120 grammes of a modified casein preparation daily, equivalent to 74·5 grammes of protein, and the other the standard diet only. These two were used as controls. The dietary supplements were administered in milk, care being taken to ensure palatability and overdosage; the latter could cause diarrhœa. The dosage of typhoid vaccine is of interest, owing to the well-known importance of using a proven antigenic vaccine which evokes good antibody response but does not cause undue reactions. The "H" antibody response was used in the assessment of the capacity of the patient to respond; the "O" antibody titre was weaker and more variable. The effect of serial doses of vaccine was followed over a period of thirty days. As previously noted a factor common to all the patients investigated was hypoproteinæmia. The authors admit that in addition the patients were suffering from various diseases which might possibly affect their capacity to respond to nutritional or immunological stimuli. This was offset by including in each group a similar number of patients suffering from the same disease. Another point which helps to validate the work is that persons with a normal blood protein level showed an antibody response far in excess of that found in any of those with hypoproteinæmia, thus illustrating the great importance of adequacy of the blood protein in the resistance to disease. The authors concluded that patients with a disturbance of protein metabolism sufficient to lower the serum albumin appreciably showed also a corresponding impairment of antibody production as estimated by their response to an efficient antigen. Supplementation of their diet with lactalbumin hydrolysate or a preparation of casein produced a definite increase in the antibody production, though this did not reach the heights observed in persons with normal blood protein

[1] *Archives of Internal Medicine*, April, 1949.

values under comparable conditions. It was found that all patients did not show a higher blood protein level after dietary supplementation. Possibly the factor of absorption is involved here; it is yet another illustration of the many variables in response to treatment which are so often a source of perplexity or dissatisfaction to both doctor and patient. The authors could find no difference between the effectiveness of lactalbumin hydrolysate and the casein preparation they used.

This work is interesting, as it supplies another link between the experimental and the clinical observations on the connexion between the reduction of power to produce antibodies and protein deficiency. Paul R. Cannon, in discussing the results, pointed out that the reduction of blood protein levels in the patients studied was relatively slight compared with those produced in animals for experimental purposes, and it was extremely interesting that readily measurable differences in response to an antigen were related to these less striking chemical variations in the plasma. It was, of course, admitted that resistance to disease could not be measured wholly by demonstrable antibodies. This work emphasizes again the importance of remembering that the protein level of a sick man's plasma should not be allowed to drop below average figures. Fortunately practical dietary methods of accomplishing this are becoming more readily available.

DIPHTHERIA IN GREECE.

OPTIMISTS may once have thought that the battle against diphtheria was practically won, but they reckoned without war and all it does to negate the hard-won blessings of peace. The pædiatric clinic of the Medical School of the University of Athens, noting an increase in diphtheria in the winter of 1945, during which over 350 children were treated in the Children's Hospital, was not unprepared for a still greater outbreak in the following year. From April, 1946, to April, 1947, the Children's Hospital of the National University treated 551 patients. A full account of this epidemic has been given by C. Choremis, N. Zervos, K. Padiatellis, P. Papadimitropoulos and M. Nikolettou, of Athens.[1] Past records show that the first recorded epidemic in Athens was in 1872. Since then only sporadic cases were recorded, and the epidemic here described produced in two years a number of cases which amounted to one-third of those treated in the last twenty years. The disproportion is now really greater on account of the difficulties in transport and communication during the recent unhappy years. The authors' patients were drawn mainly from Athens, the Piræus and neighbouring settlements. Nearly half the patients suffered from the ordinary pharyngeal type of the disease, but 34% had the purely laryngeal form, and another 13% the mixed pharyngeal and laryngeal variety. Comparison with the figures of previous studies of the disease in Greece shows that the percentage of laryngeal forms in this epidemic tallied with that observed in previous outbreaks, and also with that found during the following year, 1946-1947. Nasal diphtheria was observed in only a little over 2% of the patients. It is perhaps surprising that post-diphtheritic paralysis was observed in only one patient in this series. Most of the patients were admitted to hospital on the third day, followed in order by those admitted on the second and fifth, so that most of them came under treatment with reasonable promptness. The average number of days in hospital was only 7·3 per patient; this makes one wonder if post-diphtheritic paralysis may have occurred rather more frequently than the authors' records show. The question of previous immunization was investigated, and it was found that only four patients out of 551 had been so treated. All of these children had mild attacks. From the point of view of treatment the greatest interest centres round the methods adopted in the laryngeal form of the disease and the dosage of antitoxin. Intubation was performed in the treatment of 66 out of 262 patients: 44 patients required this procedure immediately on admission to hospital, seven others within 24 hours, and five more within 36 hours. This procedure was not effective for 25 children, who required tracheotomy. The authors remark that the gravity of the epidemic is shown by the number of children of ages up to three years who required mechanical measures of some kind. Of the 66 patients for whom intubation was carried out, 18 died.

The authors remark on the great differences of opinion which have existed concerning the dosage of antitoxin. They comment on some of the earlier scales of dosage, based on pharmaceutical habits of reckoning dose by age, and the later methods, based on the risk entailed by the circumstances of the attack rather than on any considerations of age or weight. They themselves agreed to use large doses. In 79 cases the gravity of the symptoms required intravenous administration of antitoxin, which was usually of the concentrated type. Consideration of recent work on the subject led them to give penicillin simultaneously with the antitoxin. It was hoped thereby to reinforce the action of the antitoxin and also to combat secondary infection of the respiratory tract, particularly when tracheotomy had been necessary. A future study is to be published by these authors on the non-diphtheritic acute laryngo-tracheo-bronchitis of Chevalier Jackson. They have no doubt of the value of penicillin, especially in controlling the complication of bronchopneumonia.

The mortality in this series was 5·8%. Of the 32 children who died, 19 had the laryngeal form of the disease, and it was noted that the highest mortality rate occurred in children admitted to hospital on the third or fourth day, or later. The mortality after intubation and that after tracheotomy were practically the same. The authors conclude, on reviewing their experiences, that their results were satisfactory, owing to the use of large doses of serum combined with penicillin. Exact details are not given. They consider that the chief value of penicillin was in controlling secondary infection, and noted this action particularly in children who had tracheotomy performed. Ouabain was used when the symptoms pointed to myocardial involvement and circulatory collapse. The authors think that the drug has been of value, and in dosage of 0·33 milligramme daily caused no toxic effects. Some of the conclusions reached by the authors may not be based on sound statistical considerations, and they do not always give precise and controlled information, but they present evidence of some of the evil effects of war and revolution, and of the measure of relief that can be given from the ravages of that other grim horseman, pestilence.

[1] *American Journal of Diseases of Children*, April, 1949.

THE TREATMENT OF SCARLET FEVER.

THE separation of that immune globulin fraction of pooled human plasma which is known as γ globulin stirred up fresh interest in the handling of the common infectious diseases of childhood. It has become well known in the prophylaxis of measles, and its clinical indications have been studied by a number of investigators in other directions. A recent series which is of importance, because of its considerable size and controlled study of the patients, has been the subject of a publication by John F. Landon and Lieutenant Commander S. J. Jackson.[1] It will, of course, be realized that in speaking of the diseases of childhood we must also consider their incidence and effects upon adults, who are so often involved in epidemics. The patients in the present study were seen in a civilian hospital and also in one under military control. The group under military control comprised trainees recently inducted into the service after the usual complete physical selection; they were therefore of a robust and healthy type. The civilian patients on the whole were of a less privileged class, and their standards of health and nutrition were not so high. The service trainees were mostly about eighteen or nineteen years of age, while the others were chiefly children of about seven or eight years of age. The severely ill children all received a specific form of treatment, either γ globulin or scarlet fever streptococcus antitoxin. No special treatment was given to the mildly ill. The service patients were treated by various agents,

[1] *American Journal of Diseases of Children*, July, 1948.

including γ globulin, antitoxin, human immune serum and sulphadiazine. From this material conclusions were reached as to the value of various methods of treatment in reducing the toxicity of the disease itself and in preventing or controlling complications. As the total number of cases was 1667 the results are worthy of serious attention.

The effect of γ globulin on the children was very satisfactory; nausea, vomiting and prostration subsided quickly, the temperature fell and the rash faded within forty-eight hours. The results from antitoxin were not so striking, but satisfactory in a majority. The service patients reacted equally well to the globulin, and rather better than the children to the antitoxin. The results with other methods and the success or otherwise in controlling complications are best stated in a summarized form. As 367 patients were treated with γ globulin and the general effect of this was very good, the average dose used, 40 millilitres, seems to have been effective. Streptococcus antitoxin also had a favourable effect on the primary symptoms, whether used in doses of 9000 or 27,000 units, but post-critical rises in temperature were observed, which were thought to be due to a serum reaction, in spite of the high degree of purification of the product. When we turn to the consideration of complications the position is not so good. No difference was found in the incidence of complications in the patients severely ill, whether they received antitoxin or γ globulin, though twice as many septic complications occurred in patients who were treated symptomatically as in those given globulin. Among the service patients none of those treated with globulin had late complications, but in a group three times the size comprising those who were treated with human immune serum or sulphadiazine a significant number of cases of rheumatic fever and glomerulonephritis occurred later. In a small series of patients receiving γ globulin for a mild attack no late complications were observed, though these did occur in other patients treated by other methods. Follow-up investigation seemed to show that γ globulin was effective in preventing late complications.

The authors conclude that γ globulin seems to be the most effective agent for the treatment of scarlet fever at the present time, but they are careful to state that no entirely reliable specific agent exists as yet. It has the advantage that its titre of scarlet fever streptococcus antitoxin is three to five times that of human pooled immune serum, and, used by intramuscular injection, as it was in this series, it produces no reaction. Prepared scarlet fever antitoxin appeared also to have a modifying effect on the disease, but it did not appear to prevent late complications, and has the drawback that reactions and sensitization are more likely. The high percentage of patients with mild forms of the disease who had complications is important. It seems as if further work on the production of a specific would be welcome for this reason alone. The authors are engaged in an inquiry into the value of penicillin. The amount of work necessary to allow reliable conclusions to be drawn is evident in such inquiries, but in γ globulin we appear to have an agent of value; its most effective dosage and the possibility of making it equally safe for intravenous use are questions for the future.

TWITCHING OF THE EYELIDS.

INVOLUNTARY twitching of the eyelids is a common and annoying phenomenon. It is one form of myokymia, twitching of isolated muscle fasciculi or segments, which occurs also, though less frequently, in the calves, thighs, arms, forearms and hands, and is not associated with muscular atrophy or weakness. Probably it is at least precipitated by overwork, excessive fatigue and debilitating factors. It is often ignored, especially when of minor degree, but, as is pointed out by Isador Givner and Norman S. Jaffe,[1] if it occurs in the eyelids and continues over long periods of time, it produces a psychological response which, by creating a vicious circle, has a tendency to tense rather than to relax the individual. In an attempt to combat this Givner and Jaffe have treated fifteen patients with quinine, which has a weak curariform action. They gave five grains of quinine hydrochloride three times a day for three days, after having dealt with any ætiological factors amenable to treatment. They also checked the auditory nerve and hearing for any factor which might contraindicate quinine administration. In a preliminary report, they state that all fifteen patients obtained relief, the twitching being abolished completely in nine cases. In some cases, the frequency of the twitching diminished and disappeared only after longer periods of treatment. In some cases, the twitching was aggravated before treatment by sneezing and yawning; this condition was alleviated. It is not certain how this effect is produced. Givner and Jaffe discuss it at some length, but it seems that it is probably due to the weak curariform action of the quinine. As a matter of interest two other cases of a different type are quoted, in which quinine in the same dosage produced relief: one was a case of spasmodic contraction of both stapedius muscles, which was causing audible clicking with much distress and inability to sleep (the clicking was not subjective as the examiner could hear it at a distance of three feet), and the other was a case of spastic entropion. The whole subject is one of considerable interest even if it is not one of great magnitude. Further investigation is yet needed of the related pharmacological action of quinine, but from the clinical standpoint the treatment warrants further trial. Quinine is not a dangerous drug if used with discretion, and the treatment, if it was substantiated, could be very useful, provided that its symptomatic nature was appreciated and more fundamental ætiological factors were not overlooked.

[1] *American Journal of Ophthalmology*, January, 1949.

BRONCHOSCOPIC STUDIES IN PRIMARY TUBERCULOSIS.

THE term epituberculosis is used to describe a relatively mild febrile illness occurring in children during primary tuberculous infection and particularly associated with the appearance in the lungs of radiographic shadows which later gradually disappear. Some confusion exists regarding the application of the term and the mechanism producing the radiographic shadows, and certain authorities consider that the use of the term should be discontinued. However, a considerable literature has accumulated around the term and the related phenomena, and it cannot very well be abandoned out of hand. Perhaps it will fade out of use when the phenomena are fully explained and their place in the picture of tuberculosis is understood. James H. Hutchison,[1] of Glasgow, has made a contribution towards clearing the confusion in a report of bronchoscopic studies carried out on 30 children with primary tuberculous infections. In 18 cases evidence of active primary tuberculous infection was associated with sharply outlined radiographic shadows in the lung fields, lobar or segmental in extent, but without mediastinal or tracheal displacement; the clinical and radiological findings, Hutchison states, were such as to justify a diagnosis of epituberculosis. In another 10 cases the clinical and radiological findings were similar to those of the first group and in addition there was present mediastinal or tracheal shift; obstructive emphysema also was found in two cases. The remaining two patients were suffering from uncomplicated bronchiectasis which had complicated a healed primary tuberculous infection. It would not be profitable to describe here the detailed bronchoscopic findings, but it may be stated briefly that among the 28 patients with active pulmonary tuberculosis, in nine cases evidence of local pressure by lymph glands on the bronchial wall was present; in five cases a lymph gland had eroded into the tissues of the bronchial wall, but had not perforated the mucous membrane; and in 12 cases the mucous membrane had been eroded. In only two cases of the 28 was there no evidence of bronchial obstruction; these two exceptions Hutchison regards as indicative of the diagnostic limitations of bronchoscopic examination, and he considers that the general findings

[1] *The Quarterly Journal of Medicine*, January, 1949.

indicate that in a majority of cases of epituberculosis an essential factor is bronchial obstruction with absorption collapse.

Three main causes have been advanced to explain the phenomena of epituberculosis since it was first described in 1920: non-tuberculous pneumonia, a true tuberculous process affecting the lung parenchyma, and absorption collapse due to bronchial obstruction by enlarged hilar lymph glands. The first view is not now regarded as tenable; the second and third views have much evidence to support them. Hutchison believes that his bronchoscopic findings fully support the third view, but do not exclude the second. His general summing-up is to the effect that the concept of epituberculosis as a state of absorption collapse with, in some instances, superimposed resolving parenchymal tuberculosis enables the views of those who have regarded epituberculosis as identical with pulmonary collapse to be reconciled with the views of those who have described a non-caseating tuberculous bronchopneumonia (and he quotes a lengthy list of supporters for each view). At the same time it indicates that absorption collapse is the essential pathogenesis of epituberculosis. Another finding of interest, deduced from the examination of the two patients with healed primary tuberculosis, who were suffering from bronchiectasis, is that epituberculosis may, on occasion, leave permanent damage of some severity, although it is not known how frequently. As a final point Hutchison suggests that it is possible in most cases of epituberculosis to demonstrate the presence of absorption collapse, which need not, however, be associated with much diminution in the volume of the affected part of the lung. Segmental collapse will be demonstrated only by the use of lateral and oblique radiographic views as well as antero-posterior (or postero-anterior), and accurate interpretation requires a knowledge of bronchial anatomy. The underlying bronchial occlusion and its nature can be demonstrated by tomography, lipiodol bronchography and bronchoscopy, which is, according to Hutchison, virtually free from risk and, moreover, enables the physician to exclude pulmonary collapse due to inhalation of a foreign body. This paper may not settle the question of epituberculosis for those who lean towards other views than those put forward by Hutchison, but it certainly provides valuable data. Full clinical and bronchoscopic details are given for each individual patient investigated, and a group of excellent coloured illustrations adds to the paper's usefulness and interest.

SPONTANEOUS REMISSIONS OF ACUTE LEUCHÆMIA.

THE importance of recognizing that spontaneous remissions may occur in the course of acute leuchæmia was pointed out in these columns on July 31, 1948, in a reference to the work of Farber *et alii* with the folic acid antagonist "Aminopterin". Recorded instances of such remissions have been collected by R. F. Birge, A. J. Jenks and S. K. Davis,[1] primarily to constitute a control group, which may be compared with cases of drug-induced remission. It appears that in addition to a case reported by Birge, Jenks and Davis, only ten cases of spontaneous remission have been reported since 1931 and none have been found in the literature before that year. In the case reported by Birge *et alii*, the patient was a woman, aged thirty-three years, who became affected by acute leuchæmia in the seventh month of pregnancy. Symptoms of eclampsia occurred and she was prematurely delivered of a non-viable infant, in which no evidence of leuchæmia was found at autopsy. After delivery, the patient improved rapidly and was in good health for twenty-one months; then the clinical and hæmatological picture of acute leuchæmia recurred and the patient died. During the remission, cytological evidence of leuchæmia in the sternal marrow and in the peripheral blood disappeared. The administration of radioactive phosphorus, in an attempt to induce a second remission, was followed by reduction in the leucocyte and thrombocyte counts without clinical evidence of improvement. It is interesting to note that this patient's history conforms to a clinical picture broadly common to all the recorded cases of spontaneous remission. In every case there is a febrile onset and in all but one mucous membrane involvement has occurred at some stage during the course of the disease; splenomegaly and lymphadenopathy occur less frequently. Initially, severe anæmia, leucopenia and thrombocytopenia are observed. Remission follows, lasting for as long as twenty-one months or for as short a period as two months, being characterized by apparent restoration of health, by disappearance of demonstrable lymphadenopathy and splenomegaly, and by return of peripheral blood and bone marrow pictures to normal or nearly normal. Suddenly fever and other clinical manifestations of acute leuchæmia reappear; lymphadenopathy and splenomegaly, if previously present, return. The leucocyte count rises rapidly in most instances, and evidence is again apparent of acute leuchæmia in peripheral blood and bone marrow. Death ensues rapidly. There are individual variations, but this is the broad pattern formed by the course of the disease. In one recorded case, two remissions occurred, but the outcome was still fatal. There was wide variation in classification of the eleven cases, despite the similarity of the clinical manifestations: in four cases the disease was classed as monocytic, in three as lymphatic, in two as myelogenous and in two simply as acute leuchæmia. There was no recorded parallel to the association of pregnancy and remission found in the case reported by Birge *et alii*, and they state that the experience of others has been that the course of acute leuchæmia is not significantly altered by termination of pregnancy. The remissions induced with "Aminopterin", as reported by Farber *et alii*, appear to have been as dramatic as those which occur spontaneously, and Birge and his colleagues state that ideally, remissions induced by "Aminopterin" or by other means should simulate the spontaneous remissions described. They do not elaborate this point, and speculation on significant relationships between the two types of remission is beset with pitfalls. The important points seem to be that one should have the fact of spontaneous remissions in mind in assessing any allegedly effective therapy and maintain the detailed comparison of the respective courses of the two types of remission in the hope that a vital clue may be uncovered.

[1] *The Journal of the American Medical Association*, June 18, 1949.

A CANADIAN COURSE IN AVIATION MEDICINE.

AVIATION MEDICINE is one of the new specialties which require very exact knowledge but for which few teaching facilities exist, especially in peace time. A five-day course, claimed to be the first of its kind in any country, has recently been held in Canada, being attended by 32 civilian doctors who carry out the periodical flying-fitness examinations required of private and commercial air-pilots. Facilities for the school were provided by the Royal Canadian Air Force Institute of Aviation Medicine and Canada's leading experts on this subject were the instructors. The lectures covered air-sickness, oxygen requirements and supply, air transport of the sick, night vision, the latest data in aviation medical research and the assessment of pilots' physical and mental ability. Anomalies inevitably arise when examinations such as those required for pilots' licences are carried out by civilian practitioners occupied only part-time in work of this type; the purpose of the new training plan is to establish a uniform pattern of assessment across the nation and to encourage the granting of licences to pilots whose border-line disabilities (for example, a missing finger) would not affect their efficiency in the air. Similar courses are planned to take place in the next two years for the other 200 Canadian doctors who are authorized to examine the 6500 flyers holding pilots' licences in Canada and the hundreds more who are licensed each year. This enterprising scheme should return good dividends and will no doubt be watched with interest and emulated elsewhere.

Abstracts from Medical Literature.

PATHOLOGY.

Chondromyxoid Fibroma of Bone.

HENRY L. JAFFE AND LOUIS LICHTENSTEIN (*Archives of Pathology*, April, 1948) state that the tumour described and called chondromyxoid fibroma of bone seems not to have been generally recognized in the past as a distinctive neoplasm, although it appears likely that in single instances it has been reported as enchondroma and myxoma, or their cancerous counterparts. The authors' interpretation of the lesion is that of a peculiarly differentiated connective-tissue tumour exhibiting in the course of its evolution certain chondroid and also myxoid traits which hall-mark the lesion cytologically. It is composed basically of cells lying loosely in a myxoid intercellular matrix, which, as the tumour matures, may undergo substantial collagenization. The tissue of any particular specimen may also come to simulate cartilage tumour tissue in some or many fields, and in its gross appearance it likewise bears a certain resemblance to cartilage. The authors have encountered the lesion thus far only in one or another bone of a lower limb, specifically, in the femur, the tibia and some of the bones of the foot. Within the femur or the tibia, the lesion was found consistently in the metaphyseal area adjacent to the knee joint. Also, in these bones, the lesion did not extend across the entire width of the metaphysis, but did erode and even substantially destroy the local cortex, causing the contour of the affected area of the bone to become bulged. In most instances the expanded contour was outlined, in part or throughout, by a thin shell of bone newly deposited by the periosteum. Where a demarcating cortical shell was absent, it was evident that the tumour was still contained by the periosteum and the overlying parosteal connective tissue. Along its inner surface the tumour is usually bordered by a zone of sclerosed bone. Within the bones of the foot the lesion likewise displayed a tendency to be well demarcated and to have an eccentric juxtacortical position, although in one instance (involvement of a metatarsal bone) it did come to expand and replace virtually the entire bone.

Diabetes and Uræmia Diagnosed at Autopsy.

HANS N. NAUMANN (*Archives of Pathology*, January, 1949) describes the value of rapid tests for the sugar, acetone and urea contents of cerebrospinal fluid, which may be conveniently performed at the autopsy table, for the establishing of a diagnosis of diabetes and uræmia after death. Post-mortem cerebro-spinal fluid glucose levels of 200 milligrammes or more per hundred millilitres generally indicate severe diabetes, and simultaneous presence of acetone is evidence of diabetic coma, which may be accepted as the primary cause of death. Post-mortem cerebrospinal fluid urea levels of less than 100 milligrammes per hundred millilitres will rule out renal insufficiency in the presence of renal lesions. Urea levels of more than 200 milligrammes per hundred millilitres under certain conditions may be accepted as evidence of uræmia sufficiently severe to represent a major factor in the causation of death. The importance of post-mortem analysis of urine in cases of diabetes and renal damage is also pointed out.

Fibrinolysin and the Fluidity of the Blood Post Mortem.

R. H. MOLE (*The Journal of Pathology and Bacteriology*, July, 1948) has demonstrated a fibrinolysin in over 90% of samples of fluid and incoagulable cadaver blood, all of which were free from fibrinogen. The appearance of the lysin was considered to be part of the body's general reaction to injury. This accounted for its presence in the blood after death from a wide variety of causes, and for the frequency with which fluid and incoagulable blood was found at autopsy. The fibrinolysin failed to appear after death from infections and cachexia, and this is the reason why in such cases the blood was found to be coagulated at autopsy. The fibrinolysin is probably produced by the endothelial lining of the vascular channels and body cavities. Cadaver fibrinolysin is a globulin with an optimum pH on the alkaline side of neutrality. Although it lyses fibrin it does not appear to affect fibrinogen. It differs from plasmin and the pancreatic proteinases, but may be related to the skin proteinase of Beloff and Peters and to the spontaneously active fibrinolysin of Macfarlane.

Leiomyoma of the Iris.

KEVIN O'DAY (*The British Journal of Ophthalmology*, May, 1949) reports in detail the histology of leiomyoma of the iris. The tumour described occurred in a female patient, aged sixty-five years, who had noticed loss of vision in the right eye over the previous twelve months. Clinically the most likely diagnosis appeared to be unpigmented melanoma. The author reviews other cases reported in the literature and notes that in all cases the tumour was situated in the lower half of the iris. He suggests that the tumour had arisen near the fœtal fissure and that origin of such tumours may be traced to a defect arising at the time of its closure.

Epithelial Lesions in the Respiratory Tract in Human Influenzal Pneumonia.

M. STRAUB AND J. MULDER (*The Journal of Pathology and Bacteriology*, July, 1948) have investigated various cases of clinically suspicious influenzal pneumonia encountered during the 1939-1947 period, as well as a case of virologically confirmed interpandemic influenza occurring in 1941, and have confirmed to a certain extent the observations of Askanazy and of Winternitz *et alii* on epithelial lesions of the trachea and bronchi in cases of influenza occurring during the 1918 pandemic. A special autopsy technique for the trachea and lungs in influenza, necessary for the demonstration of these lesions, is described. The authors state that the epithelial lesions, which are more or less identical with those described in mice and ferrets, consist in the disappearance of the goblet and ciliated columnar cells, the basal-cell layer being preserved and subsequently regenerating to stratified (undifferentiated) epithelium. In all but one case the epithelium of the small bronchioles was found intact, even in a case in which there was purulent bacterial bronchiolitis. This may constitute a difference from pandemic influenza, in which Winternitz *et alii* found necrosis of the bronchiolar epithelium also. The epithelial lesions now described are considered by the authors as being caused by the action of influenza virus. An alternative explanation of the epithelial lesions on the basis of bacterial toxic action cannot be completely refuted. Further combined virological, bacteriological and pathological investigations are necessary to determine the significance of these changes.

Experimental Peanut Oil Pneumonia.

W. G. GOBBEL (*American Journal of Diseases of Children*, February, 1949) states that lipid pneumonia is produced in rabbits by intratracheal injection of peanut oil. The initial response is an outpouring of polymorphonuclear leucocytes, erythrocytes, macrophages, fluid and a few small round cells into the alveolar spaces. Within ten days this exudate is replaced completely by numerous oil-containing macrophages. Although macrophages persist in large quantities in the alveoli for seventy-two days, there is no apparent injury to the parenchyma of the lung except in those few cases in which secondary infection occurs. The death rate at the end of seventy-two hours among animals which have received at least two millilitres of peanut oil injected intratracheally is 6·6%. The immediate outpouring of fluid, erythrocytes and polymorphonuclear leucocytes in the alveolar spaces is thought to be due to the presence of free fatty acid in the peanut oil, but not in such concentration as to cause necrosis of the parenchyma of the lungs. Peanut oil is sufficiently irritating to provoke a continued macrophage response. The authors state that the results of the experiment emphasize the absence of "marked toxicity" of peanut oil in the rabbit lung and support the clinical observations of Richards and of Gittens, who reported a low mortality rate among children following aspiration of peanut kernels.

Carcinoid Tumours of the Intestine.

O. F. GRIMES AND H. G. BELL (*Surgery, Gynecology and Obstetrics*, March, 1949) trace the origin of carcinoid tumours from Lubarsch (1888) to Oberndorfer (1907), who was responsible for the term "carcinoid". They discuss the work of Gosset and Masson in relation to the affinity of the intestinal chromaffin tissue for the ammoniacal silver salts and the coining of the term "argentaffin" to describe carcinoid tumours. They state that because the Kultschitzky cells are more common in the appendix than elsewhere in the intestine, carcinoid tumours are more common in that organ. The incidence is next highest in the terminal part of the ileum because of a high incidence of the Kultschitzky cells. Appendiceal carcinoid tumours occur usually in young people and are more commonly seen in females; they do not appear to metastasize, but the authors think that this is due to the fact that the tumours produce a pathological condition which is treated early by removal. The growth and histological characteristics of the tumour in any location are identical and therefore the benignity of appendiceal carcinoid tumours is more apparent than real.

Elsewhere in the gastro-intestinal tract carcinoid tumour is likely to assume malignant characteristics manifested by metastasis, most of which is either to the regional lymph glands or to the adjacent peritoneum or mesentery. Also, in the small intestine these tumours occur mostly in older people, and the multiplicity of primary lesions is in contrast with the single primary nodule occurring in the appendix in the lower age groups. The authors call attention to the four most common signs and symptoms noted in carcinoid tumours of the small bowel; the tetrad of intermittent episodes of small-bowel obstruction associated with abdominal pain, diarrhœa and loss of weight is so common and so characteristic that consideration of carcinoid tumour is strongly advised when this syndrome appears.

Cardiac Lesions in Rabbits.

R. H. MORE, D. WAUGH AND S. D. KOBERNICK (*The Journal of Experimental Medicine*, May, 1949) studied cardiac lesions produced in rabbits by massive injections of bovine serum α globulin. Focal granulomatous lesions were found in nine out of seventeen animals, and in four of them the valve itself was affected. Two animals had lesions in the coronary arteries. The lesions were in some instances comparable to those described by other authors, and also to some spontaneously occurring lesions in rabbits. The authors were unable to agree that these lesions were identical with those found in association with human rheumatic fever, but think that the experiments warrant further study.

MORPHOLOGY.

Influence of Mechanical Factors on Bone.

W. TOWNSLEY (*American Journal of Physical Anthropology*, March, 1948) sets out to show that Wolff's law holds good for the arrangement of bone substance at each stage in the changing and evolving structure of the femur throughout the vertebrate kingdom, and in the growing human femur, in which the mechanically efficient architecture appears at the age at which weight-bearing and walking begin. He states that this law also applies to bone growth associated with pathological conditions. The present investigation is a radiological examination of the structure and development of the cortical and cancellous bone in the femur, both in the human subject at different periods of life, and in animals representing successive evolutionary stages. The internal architecture and external shape of the femur at various stages of human development have been correlated with the appearance of the corresponding groups of bony trabeculæ on the phylogenetic scale, and the dependence of the architecture and external shape on changing mechanical requirements has been demonstrated in both ontogenetic and phylogenetic development. Femora were obtained from fœtuses whose ages were three months, five months, seven months and eight months, from infants and children whose ages were one month, one year, fifteen months, two and a half years, four years, eight years and ten years, and from one adult, the last being used to show the final form. The authors state that there is a continuous change in the form of the bony material of the femur throughout the growth period. As the bone enlarges in both longitudinal and transverse dimensions, the processes of absorption and reconstitution of the bone element proceed together in the compact and cancellous tissues. The architecture of the internal trabeculæ undergoes a change so that the original almost parallel trabeculæ of the fœtal and early post-natal femora are absorbed by the end of the first year and the new cross-braced systems of bony trabeculæ in the head and neck are laid down. Further, with the progressive decrease in the angle of the neck throughout childhood, there is simultaneous absorption and deposition of bone, on mechanical principles, in the correct places, both in the external compact tissue of the neck and in the internal trabeculated plates. The internal architectural features conform to the change in external form while still retaining their general pattern and efficiency as supporting structures.

Double Aortic Arch.

C. W. D. LEWIS AND J. PARRY (*The Anatomical Record*, August, 1948) describe a double aortic arch and note similar cases in the literature. They state that this condition is comparatively rare and only about forty cases had been reported up to 1936. The specimen described was discovered in the course of routine dissection of a male subject, aged fifty-two years. The authors state that double aortic arch has been suspected clinically on a number of occasions, but that it is usually symptomless and the majority of cases reported have been found in the course of routine dissection.

Observations on the Foramen of Magendie.

MURRAY L. BARR (*Brain*, September, 1948) describes the results of examination of the foramen of Magendie in 118 brains. He states that the foramen varies in size. In 3% of cases the foramen was minute, being less than one millimetre in diameter. In one case it was lacking. In the majority of cases the foramen was of variable, but considerable, size with an average size of 16 square millimetres.

Demonstration of the Coronary Arteries with "Nylon".

A. WAGNER AND C. A. POINDEXTER (*American Heart Journal*, February, 1949) describe a technique for the preparation of corrosion specimens of the coronary arteries, "Nylon" being used as the injection mass.

Innervation of the Shoulder Joint.

E. GARDNER (*The Anatomical Record*, September, 1948) states that the innervation of the shoulder joint has been studied less than that of the hip, knee and elbow, and that there has been no investigation of the distribution of the nerves after they enter the capsule. In the present investigation, the nerve supply of the shoulder joint was studied in dissections and in serial sections of fœtal joints. The author states that the articular nerves arise from the axillary, supracapsular and lateral anterior thoracic nerves, from the posterior cord of the brachial plexus, from sympathetic ganglia and possibly from the radial nerve. Details are given of the course and distribution of these nerves. Most of the articular fibres probably supply blood vessels in the capsule and neighbouring bone. The fibrous layer of the antero-inferior and antero-superior regions of the capsule contain numerous small bundles of nerve fibres.

Pituitary Concretions and Mesothelium.

W. M. SHANKLIN (*The Anatomical Record*, September, 1948) has systematically examined complete serial sections of 100 human pituitaries from individuals between birth and the age of eighty-six years for the mesothelium and mesothelial concretions. The youngest specimen in which mesothelium and mesothelial concretions were observed was from a boy, aged four years. No difference was found in the incidence of mesothelial concretions in the two sexes. In general those pituitaries with abundant mesothelium had numerous concretions. The number of pituitaries with concretions did not increase after the age of twenty years; but in those pituitaries in which they were present, the concretions were more numerous in old age. The presence of mesothelium and mesothelial concretions chiefly about the upper aspect of the pituitary is explained on an anatomical basis, while their presence deep in the pituitary is given an embryological interpretation. According to the author's interpretation most of the pituitary epithelial islets of earlier writers are areas of mesothelium which are derived from the meninges and are not derivatives of Rathke's pouch. The similarity between the areas of mesothelium and the mesothelial concretions of the pituitary and those of the meninges is stressed.

Camper's, Scarpa's and Colles's Fasciæ.

C. E. TOBIN AND J. A. BENJAMIN (*Surgery, Gynecology and Obstetrics*, May, 1949) state that the present concept of an outer fatty (Camper's) fascia and an inner membranous (Scarpa's-Colles's) fascia in the subcutaneous tissue over the ventral abdominal wall and in the perineum, and their role in directing and limiting the spread of extravasates, is not justified for the following reasons. First, there are many inconsistencies in the anatomy texts as to the structure and continuity of these layers and their relation to the cutaneous nerves and vessels; this may be related to the fact that Camper, Scarpa and Colles did not describe these layers as they are currently defined. Secondly, microscopic and macroscopic studies of sections from these regions show that the subcutaneous tissue is made up of only one layer, consisting of strands or sheets of collagenous and elastic fibres surrounding deposits of fat; this is similar to the structure of this tissue in other areas of the body. Thirdly, examination of sections taken and dissections made in real and simulated cases of extravasation from the penile urethra demonstrate that the extravasates are within the one common layer and are not limited by a deep membranous (Scarpa's-Colles's) layer. The authors consider that the attachment of the collagenous and elastic fibres to the deep fascia or periosteum of the body wall, as well as the change in direction of these fibres, and the compactness or looseness of the one subcutaneous layer, account for the direction and limitation of the spread of extravasates.

British Medical Association News.

SCIENTIFIC.

A MEETING of the New South Wales Branch of the British Medical Association was held on April 28, 1949, at the Robert H. Todd Assembly Hall, British Medical Association House, 135 Macquarie Street, Sydney, DR. J. KEMPSON MADDOX, the President, in the chair.

Otogenic Brain Abscess.

DR. VOLNEY BULTEAU read a paper entitled "Otogenic Brain Abscess" (see page 423).

DR. GILBERT PHILLIPS read a paper entitled "Otogenic Abscess" (see page 426).

DR. EDGAR THOMSON said that he had one or two points to raise. First, both speakers had rightly mentioned the use of antibiotics, and the fact that otogenic brain abscesses were often caused by Gram-positive organisms sensitive to penicillin. That statement was true; but he did not think that at the present time it was as true as they would like it to be. Every day they were facing more and more strains of Gram-positive organisms that were resistant to penicillin. Dr. Thomson sounded a warning note; the subject was one in which he was interested and on which he and his colleagues were working. He hoped that in the not far distant future some interesting information would be available. Dr. Thomson said that the widespread and unnecessary use of penicillin had presented them with a large number of Gram-positive organisms, particularly staphylococci, which were resistant to penicillin. He did not know the mechanism by which that came about; the answer to the problem had not yet been produced. He thought that they were going to see—and such things had already been seen at the Royal Prince Alfred Hospital—otogenic brain abscesses in which the organisms were resistant to penicillin. Of course, it could be said that they could fall back on streptomycin; but if streptomycin was used in the indiscriminate way in which penicillin had been used, streptomycin-resistant organisms would be produced in a very short time, and more quickly than those resistant to penicillin were produced. The second point was that, as Dr. Bulteau had said, the laboratory was unable to demonstrate or to grow an organism from the cerebro-spinal fluid. Dr. Thomson thought that the reason was that when the patient's condition had progressed to the stage at which cerebro-spinal fluid was taken for examination, the organism was not in it, but was in the cerebral tissues. Even when such abscesses ruptured and the cerebro-spinal fluid became purulent, they were still sometimes unable to demonstrate the infecting organism. He was consoled by the fact that Sir Hugh Cairns had referred to the same difficulty found at Oxford in cases of meningitis and cerebral abscess. The organisms were up top and not below; and the failure was due not so much to the use of chemotherapy and antibiotics as to absence of the organism. The third point was one raised in Dr. Bulteau's paper. There was a popular belief that the chloride content of the cerebro-spinal fluid was less than normal in cerebral abscess. It was true that until recently a low chloride content was thought to be pathognomonic of meningitis. Such a state of affairs was found in cerebral abscess; but it was more significant once the abscess had leaked and ruptured and the fluid had become purulent. If the cerebro-spinal fluid was purulent as a result of meningitis, the chloride content was nearly always normal. In several cases of cerebral abscess with secondary meningitis, the chloride content of the cerebro-spinal fluid had been as low as 650 or even 600 milligrammes *per centum*. Dr. Thomson did not know the scientific basis for what he was saying; but he regarded a low chloride content in turbid cerebro-spinal fluid as connected with cerebral abscess.

DR. E. P. BLASHKI said that from the otologist's point of view one thing always had to be kept in mind; although the difficulties in the diagnosis and cure of cerebral abscess had been shown, the otologist could do much in preventing their development by making sure that healing occurred in his operation cases. He should not be satisfied if suppuration continued in any case after a mastoid operation. Dr. Blashki's experience extended over a number of cases. Sometimes healing was incomplete and the patient was resistant to the suggestion of further operation; one such patient in two years developed a fatal cerebral abscess. Further, in performing a mastoid operation, in the past at all events, surgeons had not always been correct in their choice of procedure. In the less acute cases, in which at operation the bone was found to be sclerotic, to be content with a simple mastoid operation was to court failure. Cases occurred in which the diagnosis of acute mastoiditis was made, and in which at operation sclerotic bone was present. The condition was recurrent mastoiditis, or slumbering mastoiditis, not acute; so the performance of simple mastoidectomy was to court disaster. Referring to the existence of otogenic abscess in a symptomless form, Dr. Blashki asked how long such an abscess could remain symptomless. In symptomless cases it sometimes happened that the sudden onset of symptoms was followed by death within an hour or two; he asked whether in such cases a latent abscess had been present for years, or whether that fatal complication was a matter of days or weeks. He had never been able to answer that question. Dr. Blashki was glad to hear that results in the treatment of otogenic brain abscess were so much better than ten years previously, and he hoped that they would be better still in the future.

DR. G. C. HALLIDAY said that Dr. Bulteau's figures were interesting particularly in one respect: though cases of otogenic brain abscess were few since 1944, apparently their incidence was the same as in pre-penicillin days. It was also true that very few patients suffering from *otitis media* at the present time were given penicillin—possibly not 1%—in the course of the uncomplicated disease. Penicillin was used as a rule only in fulminating cases, or when intracranial complications were suspected. It was difficult for that reason to say what influence penicillin had had on *otitis media*. A second point of interest was that since the days of chemotherapy, the incidence of acute mastoid disease requiring operation had diminished greatly throughout the world. The main difficulty was really to know how a brain abscess started. It was not known at what period in the disease process the brain abscess developed, and once it had developed it was difficult to diagnose in the early stages; from the otologist's point of view it was masked by other more apparent symptoms. The only thing to do was to watch such patients carefully and always to be suspicious of them; but the difficulty in diagnosis must continue.

Dr. Maddox asked whether any of the psychiatrists present had had patients with unsuspected otogenic brain abscess referred to them on account of psychiatric symptoms. He thought it would be interesting to know whether in many cases such abscesses were ultimately found to be the cause of mental illness.

DR. A. T. EDWARDS said that during twenty years in the Mental Hospitals Department of New South Wales he had performed between 800 and 1000 autopsies; particular attention was paid to any subject concerning whom it was thought that an intracerebral condition might have been the cause of a psychosis. In that number of autopsies he (Dr. Edwards) had found two cerebral tumours, but no brain abscess, as a cause for a psychosis. His evidence was purely negative.

Dr. Maddox, from the chair, said that the discussion had been interesting. He thought that if the meeting had been held ten years earlier, the Section of Medicine would have been included. But now the physician could make only a minor contribution in the diagnosis, for example, between malaria and cerebral abscess, and in making an occasional neurological survey; even the latter was not so accurate or so valuable as some of the more exact methods outlined by Dr. Phillips. Referring to the change for the better shown by the figures quoted by Dr. Bulteau, Dr. Maddox said that if antibiotics or penicillin were not responsible, the change must be due to improvements in technique and treatment on the part of the neurosurgeon. Dr. Maddox asked Dr. Thomson why the chloride content of the cerebro-spinal fluid was low in cerebral abscess and meningitis. It was not a meningeal reaction. Dr. Bulteau had said that the infecting organism was apparently a Gram-positive coccus, and he thought that other flora were very rare. That was an unusual situation, and Dr. Maddox wondered whether Dr. Thomson had any explanation for it. He also wondered why it was that penicillin in large doses could not reach a primary encephalitis destined to become an otogenic abscess, and so cut short the process at the presuppurative stage. Dr. Maddox asked Dr. Phillips why he thought that an abscess grew larger after its first aspiration; he wondered whether there was some mechanical reason.

Dr. Bulteau, in reply to Dr. Blashki, said that the period of time during which an abscess might be present without causing symptoms interested him very much; he had been through much of the literature, and the whole situation seemed to be characterized by variations, the period varying from days up to almost years. Dr. Bulteau instanced the case history mentioned in his paper, in which the wife said that her husband had not spoken to her for ten years or more. Had that man had an abscess during all that long period? He could not offer any solution to the problem. To Dr. Halliday, who had asked when the infection really

started, Dr. Bulteau said that some type of feverish attack took place at the time of actual invasion of the brain; the patient reported a bout of "influenza", "malaria" *et cetera*. The origin had to be dated from the feverish attack. To Dr. Maddox, Dr. Bulteau said that the infection was nearly always mixed, but that Gram-positive cocci predominated. Frequently one did not know the organism with which one was dealing, because it could not be isolated from the cerebro-spinal fluid; perhaps after two or three days a culture of an organism such as *Proteus vulgaris* might be produced; it was then difficult to say whether it was the causal organism or not. In treatment one might be forced into using the "shotgun" method with every type of antibiotic. With regard to acute encephalitis, Dr. Bulteau said that it was his belief that that stage of the infection represented a reversible phenomenon, and provided that the antibiotic substances used could come in contact with it, the condition could return to normal. Dr. Bulteau quoted the case of a girl, aged eleven years, in whose case the evidence pointed to a temporal lobe abscess. With chemotherapy, lumbar and ventricular punctures, and a radical mastoid operation, she had gone on to complete recovery. Dr. Bulteau believed that she had had acute encephalitis which had responded to those measures.

Dr. Phillips, in reply to Dr. Blashki, said that he thought a brain abscess could undergo spontaneous cure by calcification. Such a lesion had been found at post-mortem examination and had caused no symptoms during life; it could exist throughout life. Referring to cerebral abscess as a very sudden cause of death, Dr. Phillips said that two sudden causes of that were either intraventricular rupture with blocking of the aqueduct of Sylvius with pus, or else herniation of the uncus of the hippocampal gyrus, the uncus being pushed across the tentorium and impacted. That might be precipitated by the removal of a fairly large volume of cerebro-spinal fluid. Dr. Phillips said that Dr. Halliday had reached the root of the trouble when he had asked when the diagnosis was made. Dr. Phillips felt that the diagnosis had been made only when pus had been aspirated. If pus was not aspirated, there was a serious need to proceed with air studies. He had had the experience of finally finding an abscess in the temporal lobe *post mortem*, when air studies had been omitted. Referring to Dr. Maddox's remarks about the failure of penicillin to interrupt the development of a cerebral abscess, cerebral thrombophlebitis *et cetera*, Dr. Phillips said that extremely massive œdema was present—a kind of Pott's puffy tumour of the brain—and the hemisphere in which cerebral thrombophlebitis existed had a volume much larger than normal. That central nidus of infection was protected from antibiotic attack by the large volume of fluid. In reply to the question why an abscess grew larger after it had been aspirated, Dr. Phillips said that an extrinsic factor and an intrinsic factor were at work. After aspiration an immediate and adequate cerebral decompression was produced, and within a few hours the œdema began to subside. Within twelve to twenty-four hours the ventricles could be seen returning to their normal position, giving room for the abscess to expand. The extrinsic factor was the irritating effect of the thorotrast that had been injected into the aspirated abscess.

Dr. Maddox, from the chair, said that the meeting had been valuable and had given a great deal of help in the recognition, diagnosis and treatment of the difficult and rare condition under discussion, which none the less was serious and could be tragic. The thanks of the meeting were extended to Dr. Bulteau and Dr. Phillips.

NEW SOUTH WALES BRANCH NEWS.

THE following books, pamphlets and journals have been added to the library of the New South Wales Branch of the British Medical Association during the period April 1, 1949, to August 31, 1949.

Albee, Fred H., "Bone Graft Surgery in Disease, Injury and Deformity", 1940; Allen, F. M. B., "Aids to the Diagnosis and Treatment of Diseases of Children", Eighth Edition, 1947; Austin, R. G., "Aids to Physical Chemistry", Second Edition, 1948, "Aids to Qualitative Inorganic Analysis", Second Edition, 1947.

Bailey, Hamilton, and Love, R. J. McNeill, "A Short Practice of Surgery", Eighth Edition, 1948, Volume III; Bailey, P., "Intracranial Tumours", Second Edition, 1948; Barborka, C. J., "Treatment by Diet", Fifth Edition, 1948; Batty, R. J., "Enuresis or Bed-wetting", Second Edition, 1948; Baxter, J. S., "Aids to Embryology", Fourth Edition, 1948, "Aids to Surgical Anatomy", Second Edition, 1942; Bethea, O. W., "1948 Year Book of General Therapeutics"; Birch, C. A. (Editor), "Emergencies in Medical Practice", 1948; Brailsford, J. F., "Radiology of Bones and Joints", Fourth Edition, 1948; Brews, A., "Eden and Holland's Manual of Obstetrics", Ninth Edition, 1948; Brown, R. C., "Reproduction and Survival", 1948; Bunnell, S., "Surgery of the Hand", Second Edition, 1948.

Cahn, L., *et alii*, "1948 Year Book of Dentistry"; Carling, Sir E. R., and Ross, J. P., "British Surgical Practice", 1948, Volume V; Carruthers, D. G., "Diseases of the Ear, Nose and Throat", Second Edition, 1948; Clark, W. M., "Topics in Physical Chemistry: Supplementary Text for Students of Medicine", 1948; Coke, F., and Coke, H., "Asthma", Second Edition, 1939; Collis, J. L., and Mabbit, L. E., "Handbook of Chest Surgery for Nurses", Second Edition, 1946; Compere, E. L., "1948 Year Book of Orthopedics and Traumatic Surgery"; Cooper, E. A., and Nicholas, S. D., "Aids to Biochemistry", Fourth Edition, 1948; Copeman, W. S. C. (Editor), "Textbook of the Rheumatic Diseases", 1948.

Dahlberg, G., "Statistical Methods for Medical and Biological Students", 1940; Daniels, M., *et alii*, "Tuberculosis in Young Adults: Report on the Prophit Tuberculosis Survey, 1935-1944", 1948; Devine, Sir H., and Devine, J., "Surgery of the Colon and Rectum", 1948; Doherty, M. K., *et alii*, "Modern Practical Nursing Procedures", 1949; Du Bois, E. F., "Fever, and the Regulation of Body Temperature", 1948.

"Edinburgh Post-Graduate Lectures in Medicine", Volume IV, 1944-1947, 1948; Eggston, A. A., and Wolff, D., "Histopathology of the Ear, Nose and Throat", 1947; Ewen, J. H., "Aids to Psychology", Third Edition, 1948.

Froeschels, E., "Philosophy in Wit", 1948; Fulton, J. F., *et alii* (Editorial Board), "Frontal Lobes", *Proceedings of the Association for Research in Nervous and Mental Disease*, Volume XXVII, 1948.

Gabriel, W. B., "Principles and Practice of Rectal Surgery", Fourth Edition, 1948; Gamble, J. L., "Chemical Anatomy, Physiology and Pathology of Extracellular Fluid: A Lecture Syllabus", 1947; Geschickter, C. F., and Copeland, M. M., "Tumors of Bone", Third Edition, 1949; Gibberd, G. F., *et alii*, "Queen Charlotte's Text-book of Obstetrics", Seventh Edition, 1948; Goldberger, E., "Unipolar Lead Electrocardiography", 1947; Goldman, V., "Aids to Anæsthesia", Second Edition, 1948; Gradwohl, R. B. H., "Clinical Laboratory Methods and Diagnosis: Textbook of Laboratory Procedures with their Interpretation", Fourth Edition, 1948, Volumes I, II and III; Graham, E. A., "1948 Year Book of General Surgery"; Greene, R. (Editor), "Practice of Endocrinology", 1948.

Haler, D., "Aids to Clinical Pathology", 1944; Heaf, F., and Rusby, N. L., "Recent Advances in Respiratory Tuberculosis", Fourth Edition, 1948; Hodges, F. J., and Kaplan, I. I., "1948 Year Book of Radiology".

Joske, P. E., "Law and Procedure at Meetings in Australia and New Zealand", Second Edition, 1949; Joslin, E. P., "Diabetic Manual", Eighth Edition, 1948.

Kermack, W. O., and Eggleton, P., "Stuff We're Made Of", Second Edition, 1948; Kinsey, A. C., *et alii*, "Sexual Behaviour in the Male", 1948.

Lake, N. C., "The Foot", Third Edition, 1943; Lane-Roberts, C., *et alii*, "Sterility and Impaired Fertility", Second Edition, 1948; Lennox, W. G., *et alii*, "Epilepsy", "Research Publications: Association for Research in Nervous and Mental Disease", Volume XXVI, 1947; Lowsley, O. S., "1948 Year Book of Urology".

McEwan, P., "Clinical Picture of Thyrotoxicosis", 1948; Macintosh, R. R., and Mushin, W. W., "Physics for the Anæsthetist", 1946; MacKenna, R. M. B., "Aids to Dermatology", Third Edition, 1946.

Mace, D. R., "Marriage Counselling", 1948; Maingot, R., "Abdominal Operations", Second Edition, 1948; Mair, G. B., "Surgery of Abdominal Hernia", 1948; Maxson, L. H., "Spinal Anesthesia", 1938; Means, J. H., "Thyroid and its Diseases", Second Edition, 1948; Medical Directories, Great Britain (Parts I and II, 1949), Australia (1948); Medical Register, England (Parts I and II, 1949); Mills, G. P., and Humphreys, H., "Text-book of Surgery for Dental Students", Fifth Edition, 1948; Moffatt, P. McG., "Aids to Ophthalmology", Tenth Edition, 1948; Monrad-Krohn, G. H., "Clinical Examination of the Nervous System", Ninth Edition, 1948; Murray, D. S., "Search for Health", 1948.

Naylor, A., "Fractures and Orthopædic Surgery for Nurses and Masseuses", Second Edition, 1948; Neill, R. G., "Aids to Biology", Second Edition, 1948; Newns, G. H., "Aids to Materia Medica", Third Edition, 1944; Nicholls, L., "Aids to Tropical Hygiene", Third Edition, 1946.

Oliver, J. O., "Aids to Pathology", Ninth Edition, 1948; Osmond, T. E., "Aids to the Diagnosis and Treatment of Venereal Diseases", 1946.

Papanicolaou, G. N., *et alii*, "Epithelia of Woman's Reproductive Organs", 1948; Papanicolaou, G. N., and Traut, H. F., "Diagnosis of Uterine Cancer by the Vaginal Smear", 1943; Paterson, R., "Treatment of Malignant Disease by Radium and X-rays", 1948; Piney, A., and Hamilton-Paterson, J. L., "Sternal Puncture", Fourth Edition, 1949; Portis, S. A. (Editor), "Diseases of the Digestive System", Second Edition, 1944; Primmer, J. B., "Hints on Prescribing under the National Health Service Act", 1949.

Reese, H. H., *et alii*, "1948 Year Book of Neurology, Psychiatry and Endocrinology"; Riddell, V., "Carcinoma of the Breast", 1948; Roberts, G. F., "Rhesus Factor", 1947; Roberts, L., "Aids to Public Health", Fifth Edition, 1946; Robertson, N., "Sex and Marriage", 1949; Rubenstein, I. H., "Treatise on Contemporary Religious Jurisprudence", 1948; Russell, K. F., "A Check List of Medical Books Published in England before 1600", 1947.

Schatkin, S. B., "Disputed Paternity Proceedings", Second Edition, 1947; Scott, G. E. M., "Juvenile Rheumatism", 1948; Scott, G. R., "Sex and its Mysteries", 1948; Scott-Wilson, H. W., "Aids to Bacteriology", Seventh Edition, 1946; Smith, S. E., "Aids to Organic Chemistry", Third Edition, 1948; Somervell, T. H., "Surgery of the Stomach and Duodenum", 1948; Stevenson, R. S., "Recent Advances in Otolaryngology", Second Edition, 1949; Sullivan, L., "Case Against Socialized Medicine", 1949; Sulzberger, M. B., and Baer, R. L., "1948 Year Book of Dermatology and Syphilology"; Sulzberger, M. B., and Wolf, J., "Dermatologic Therapy in General Practice", Third Edition, 1948; *Surgery, Gynecology and Obstetrics*, Index to Volumes XLI to LXXX, 1925-1945.

Taussig, H. B., "Congenital Malformations of the Heart", 1947.

University of Melbourne, Annual Reports, 1939-1946.

Wallace-Jones, H., *et alii*, "Elementary Atlas of Cardiography", 1948; Walshe, F. M. R., "Critical Studies in Neurology", 1948; Watson, L. F., "Hernia", Third Edition, 1948; Winterton, W. R., "Aids to Gynæcology", Tenth Edition, 1947.

Journals: *Electroencephalography and Clinical Neurophysiology*, Volume I, 1949; *Federation Proceedings*, Volume VIII, 1949; *Medicine Illustrated*, Volume III, 1949; *Pediatrics*, Volume I, 1948.

Correspondence.

PREGNANCY AND INTESTINAL OBSTRUCTION: A DANGEROUS COMBINATION.

SIR: On reading the summaries of ten cases as reported in THE MEDICAL JOURNAL OF AUSTRALIA of August 27, 1949, one is struck by:

1. The late results of the abdominal cure of retroversion when a similar cure can be obtained vaginally in 90% of cases.
2. Intestinal obstruction is the normal province of surgeons, and cases could be transferred to their care for early diagnosis and treatment.
3. In appendicectomy through a McBurney's incision, ligature of the stump without invagination leads to a lower mortality (Horsley and Bigger: "Operative Surgery"). I have a series of over 200 cases with this form of treatment with no mortality. H. E. Robertson, of the Mayo Clinic, says that burying of the stump of the amputated appendix is "wholly illogical and worse than that a dangerous procedure" (Horsley and Bigger: "Operative Surgery).

Yours, etc.,
J. N. R. STEPHEN, M.B., Ch.B. (Glasgow).

Darby Street,
Newcastle,
September 1, 1949.

B.C.G. VACCINATION AGAINST TUBERCULOSIS.

SIR: I have read Dr. Poynton's letter in THE MEDICAL JOURNAL OF AUSTRALIA of August 27, 1949, *re* B.C.G. vaccination against tuberculosis. I fully appreciate Dr. Poynton's point of view, and I am glad he has written emphasizing the importance of the work done in Adelaide.

A careful perusal of Dr. North's article in the journal of July 30, 1949, led me to the belief that the main object of his communication was to review the evidence in favour of B.C.G. vaccination as a preventive measure against tuberculosis, and I thought he did this very well.

I believe the work done in Adelaide was very good indeed. In over 1000 cases it showed that B.C.G. vaccination was safe and that it caused a conversion of the Mantoux reaction in 99% of the cases fully investigated. The work, however, is too recent to give any indication of its protective value. It may take five or ten years to give any real indication in this regard, and then only if we can follow up our cases and a similar number of unvaccinated "controls" subjected to the same risk of infection.

For an indication of its protective value we must at present rely upon the evidence of other workers, and I think it was this aspect to which Dr. North wished to draw attention.

Yours, etc.,
D. R. W. COWAN.

163 North Terrace,
Adelaide,
September 6, 1949.

SIR: In my letter published in your issue of September 10, 1949, I stated that the work of Miss Atkinson and her associates on B.C.G. vaccination was "the first of its kind in Australia". While that statement is correct for human vaccination, I regret that I overlooked the fact that Woodruff and Gregory in 1928 and 1929 published two articles in the *Journal of the Council for Scientific and Industrial Research*, in which they describe the preparation, testing and use of B.C.G. vaccine in the prevention of tuberculosis in cattle.

Yours, etc.,
HUGH WARD.

The University of Sydney,
Sydney,
September 7, 1949.

Post-Graduate Work.

THE MELBOURNE PERMANENT POST-GRADUATE COMMITTEE.

PROGRAMME FOR OCTOBER, 1949.

Clinical Week at the Alfred and Women's Hospitals.

THE programme of the clinical demonstrations arranged by the Alfred Hospital for October 17, 18, 19 and 20 and by the Women's Hospital for October 21 has been published previously. Attendance is by open invitation.

Lectures in Social Medicine by Professor F. A. E. Crew.

The following lectures will be given by Professor F. A. E. Crew, Professor of Public Health in the University of Edinburgh, in the Medical Society Hall, 426 Albert Street, East Melbourne, at 8.15 p.m.: Monday, October 17, "Medico-Sociological Aspects of an Ageing Population"; Friday, October 21, "Biological Aspects of Marriage"; Monday, October 24, "The Changing Emphasis in Medicine"; Thursday, October 27, "The Contributions of Genetics to Medicine". The fee for this course is £2 2s., or 10s. 6d. per lecture. Resident medical officers may attend at half-fees. Enrolments should be made with the Secretary of the Post-Graduate Committee, 426 Albert Street, East Melbourne.

Lecture in Psychiatry by Professor Alexander Kennedy.

A lecture in psychiatry will be given by Professor Alexander Kennedy, Professor of Psychological Medicine in the University of Durham, in the Medical Society Hall, 426 Albert Street, East Melbourne, on Thursday, October 20, 1949. This lecture will be given by courtesy of the Victorian Government, the British Council and the Australasian Association of Psychiatrists. There will be no charge for admission.

Refresher Week-End Course at Horsham.

A refresher week-end course will be held at Horsham on October 8 and 9, 1949. Lectures at times to be announced later will be given by Dr. R. S. Lawson on "Acute Intestinal Obstruction, with Special Reference to Strangulated Hernia", Mr. C. K. Churches on "Cæsarean Section", and Dr. V. L. Collins on "Recent Pædiatric Developments" and "Fibrositis and Rheumatism". A ward round will also be conducted. Dr. B. Hutton-Jones, Horsham, will make enrolments.

CORRECTIONS TO SYLLABUS.

Week-End Course at Hamilton.

The dates set down for the meeting at Hamilton on page 5 of the Post-Graduate Syllabus for 1949, namely, October 8 and 9, are wrong. The refresher week-end course at Hamilton will be held on November 19 and 20.

Eye Clinic.

The Eye Clinic, which was to have been held on October 7, 1949, at the Eye and Ear Hospital, has been cancelled on account of the meeting in Melbourne of the Ophthalmological Society of Australia (British Medical Association).

THE POST-GRADUATE COMMITTEE IN MEDICINE IN THE UNIVERSITY OF SYDNEY.

Lectures in Psychosomatic Medicine.

THE Post-Graduate Committee in Medicine in the University of Sydney announces that Professor Alexander Kennedy, M.D., M.R.C.P., D.P.M., Professor of Psychological Medicine, University of Durham, England, will give two lectures on "Some Aspects of Psychosomatic Medicine" at 8.15 p.m. on Monday, October 10, and Wednesday, October 12, 1949, in the Stawell Memorial Hall, 145 Macquarie Street, Sydney. Both lectures are open to the medical profession. Admission tickets are not required, but further inquiries may be made from the Course Secretary, the Post-Graduate Committee in Medicine, 131 Macquarie Street, Sydney. Telephones: BU 5238, BW 7483.

Congresses.

AN OPHTHALMOLOGICAL CONGRESS IN AMERICA.

A NOTIFICATION has been received from the Director-General of Health, Canberra, to the effect that the next annual conference of the National Society for the Prevention of Blindness will be a combined meeting with the Pan-American Association of Ophthalmology, and will be held on March 26 to 30, 1950, at the Hotel Floridian, Miami Beach, Florida.

Among the topics to be discussed at the conference are: "Current Blindness Prevention Programmes in the Countries of the Western Hemisphere"; "Trachoma"; "Industrial Ophthalmology"; "Eye Problems of School Children"; "Medical and Social Management of the Glaucomas".

The conference is open to all interested persons. Further information may be obtained from Dr. Franklin M. Foote, Executive Director of the National Society for the Prevention of Blindness, 1790 Broadway, New York City, U.S.A.

Naval, Military and Air Force.

APPOINTMENTS.

THE undermentioned appointments, changes *et cetera* have been promulgated in the *Commonwealth of Australia Gazette*, Number 62, of August 25, 1949.

NAVAL FORCES OF THE COMMONWEALTH.

Permanent Naval Forces of the Commonwealth (Sea-going Forces).

Appointment.—James O'Donoghue is appointed Surgeon Lieutenant (for short service), dated 16th May, 1949.

Citizen Naval Forces of the Commonwealth.

Royal Australian Naval Reserve.

Transfer to Retired List.—Surgeon Lieutenant-Commander Eric Leo Susman is transferred to the Retired List, dated 6th June, 1949.

AUSTRALIAN MILITARY FORCES.

Reserve Citizen Military Forces.

Royal Australian Army Medical Corps.

Major-General R. W. W. Walsh, D.S.O., V.D., relinquishes the appointment of Honorary Surgeon to His Majesty the King and is placed upon the Retired List (2nd Military District) with permission to retain his rank and wear the prescribed uniform, 1st August, 1949.—(Ex. Min. No. 107—Approved 17th August, 1949.)

DISEASES NOTIFIABLE IN EACH STATE AND TERRITORY OF AUSTRALIA AND NOTIFICATIONS FOR THE WEEK ENDED AUGUST 27, 1949.[1]

Disease.	New South Wales.	Victoria.[2]	Queensland.	South Australia.	Western Australia.	Tasmania.	Northern Territory.[3]	Australian Capital Territory.	Australia.[2]
Ankylostomiasis	*	..	1	..	*	..	..	..	1
Anthrax	*	..	..	..	..	..	..	..	..
Beriberi	*	*	*	..	*	*	..	*	..
Bilharziasis	*	..	..	..	..	..	..	..	..
Cerebro-spinal Meningitis	1	..	..	..	..	..	..	..	1
Cholera	..	..	..	..	..	..	..	..	..
Coastal Fever(*a*)	*	*	..	*	*	*	*	..	..
Dengue	*	*	*	*	*	*	..	*	..
Diarrhœa (Infantile)	..	..	7(6)	..	..	..	..	..	7
Diphtheria	14(9)	..	1(1)	1	3(3)	..	..	1	20
Dysentery(*b*)	*	..	..	..	..	..	..	..	..
Encephalitis Lethargica	..	..	..	..	..	..	..	..	..
Erysipelas	*	*	*	5(4)	*	*	..	..	5
Filariasis	*	..	..	..	..	..	..	..	..
Helminthiasis	*	..	*	*	*	*	*	*	..
Hydatid	*	..	*	*	..	*	*	..	..
Influenza	*	*	*	..	*	*	..	*	..
Leprosy	..	..	..	..	..	..	..	..	..
Malaria(*c*)	*	(*c*)	1(*c*)	(*c*)	(*c*)	(*c*)	(*c*)	(*c*)	1(*c*)
Measles	*	*	*	67(30)	*	*	..	..	67
Plague	..	..	..	..	..	..	..	..	..
Poliomyelitis	..	..	1	9(7)	..	..	..	2	12
Psittacosis	*	..	*	..	*	*	*	*	..
Puerperal Fever	..	..	..	..	..	..	..	..	..
Rubella	*	*	*	*	*	*	..	..	..
Scarlet Fever	42(24)	..	9(5)	16(13)	4(3)	8(2)	..	3	82
Smallpox	..	..	..	..	..	..	..	..	..
Tetanus	*	..	4(1)	*	*	*	*	*	4
Trachoma	*	..	*	*	*	*	*	*	..
Tuberculosis(*d*)	22(19)	..	8(7)	3(3)	8(6)	2(1)	..	1	44
Typhoid Fever(*e*)	..	..	..	1(1)	..	..	..	..	1
Typhus (Endemic)(*f*)	1	..	..	..	..	..	..	..	1
Undulant Fever	..	..	..	..	..	..	..	..	..
Weil's Disease(*g*)	*	*	*	*	*	*	*	*	..
Whooping Cough	*	*	*	30(3)	*	*	..	..	30
Yellow Fever	..	..	..	..	..	..	..	..	..

[1] The form of this table is taken from the *Official Year Book of the Commonwealth of Australia*, Number 36, 1944-1945. Figures in parentheses are those for the metropolitan area.
[2] Figures not available.
[3] Figures incomplete owing to absence of returns from Northern Territory and Victoria.
* Not notifiable.
(*a*) Includes "Mossman" and "Sarina" fevers. (*b*) Includes amœbic and bacillary. (*c*) Statistics inexact with varying practice with regard to relapses in Service cases infected overseas. (*d*) Includes all forms except in New South Wales and Northern Territory, where only pulmonary tuberculosis is notifiable. (*e*) Includes enteric fever, paratyphoid fevers and other Salmonella infections. (*f*) Cases reported include scrub, murine and tick typhus. (*g*) Includes leptospiroses, Weil's and para-Weil's disease.

ROYAL AUSTRALIAN AIR FORCE.

Reserve: Medical Branch.

The following are appointed to commissions with the rank of Flight Lieutenant: Beric Tristram Glanville-Hicks (257775), 3rd March, 1949, Douglas Forsyth Burns (277557), Max Clifford Moore (287472), 20th June, 1949.

The appointment of Flight Lieutenant A. M. V. P. Horton (257724) is terminated, 28th June, 1949.

Australian Medical Board Proceedings.

TASMANIA.

THE undermentioned have been registered, pursuant to the provisions of the *Medical Act*, 1918, of Tasmania, as duly qualified medical practitioners:

Kennard, Joyce, M.B., Ch.B., 1942 (Bristol), D.P.H., 1947 (London), Department of Health, Hobart.

Houston, Hugh Benjamin Craig, M.B., B.Ch., 1941 (Dublin), Department of Health, Hobart.

Forster, John Francis Anning, M.R.C.S. (England), L.R.C.P. (London), 1934, M.B., B.S., 1935 (London), Campbell Town, Tasmania.

Morton, Max Robson, M.B., B.S., 1947 (Univ. Sydney), Maroubra, Sydney.

The following additional qualifications have been registered:

Fay, Franklin Robert, F.R.A.C.S., 1948.

Lewis, Reginald Abbot, Dip. in Anæs., Sydney, 1948.

QUEENSLAND.

THE undermentioned have been registered, pursuant to the provisions of *The Medical Acts, 1939 to* 1948, of Queensland, as duly qualified medical practitioners:

Murray, Victor Reginald Ernest, M.B., B.S., 1941 (Univ. Sydney), Main Street, Murwillumbah, New South Wales.

McGurgan, Cyril Joseph, M.B., B.S., 1948 (Univ. Melbourne), Mater Hospital, South Brisbane.

Leggat, William, L.R.C.P., L.R.C.S. (Edinburgh), L.R.F.P.S. (Glasgow), 1948, 60 Dornoch Terrace, West End, Brisbane.

Ward, John Gerard O'Hagan, L.R.C.P., L.R.C.S., L.M.R.C.S., L.M.R.C.P., 1937 (Ireland), c.o. Dr. T. M. Webster, Railway Street, Gatton.

The following additional qualification has been registered:

Knott, Charles Henry, 22 Abbott Street, Cairns, F.R.A.C.S., 1949.

Obituary.

BRYNMOR BEVERIDGE JONES.

WE regret to announce the death of Dr. Brynmor Beveridge Jones, which occurred on August 23, 1949, at Ivanhoe, Victoria.

Nominations and Elections.

THE undermentioned have applied for election as members of the South Australian Branch of the British Medical Association:

Gliddon, Alfred Bertram Keith, M.B., B.S., 1948 (Univ. Adelaide), 8 Norman Street, Woodville, South Australia.

Bundey, John Goode, M.B., B.S., 1947 (Univ. Adelaide), 247 Prospect Road, Prospect, South Australia.

Kelman, Hilda, M.B., B.S., 1947 (Univ. Adelaide), Royal Adelaide Hospital, South Australia.

The undermentioned have been elected as members of the South Australian Branch of the British Medical Association:

Ey, Geoffrey Thomas, M.B., B.S., 1947 (Univ. Adelaide), 3 Wheaton Road, St. Peters, South Australia.

Pavy, Rosemary Dorothea, M.B., B.S., 1948 (Univ. Adelaide), 7 Rutland Avenue, Unley Park, South Australia.

Cherry, Aileen Percival, M.B., B.S., 1949 (Univ. Adelaide), 23 Brougham Place, Alberton, South Australia.

Texler, Karl Marie, M.B., B.S., 1943 (Univ. Adelaide), 88 Hutt Street, Adelaide.

Tesler, Eva, M.B., B.S., 1943 (Univ. Adelaide), 188 North Terrace, Adelaide.

Diary for the Month.

SEPT. 19.—Victorian Branch, B.M.A.: Finance, House and Library Subcommittee.

SEPT. 21.—Western Australian Branch, B.M.A.: General Meeting.

SEPT. 20.—New South Wales Branch, B.M.A.: Medical Politics Committee.

SEPT. 22.—New South Wales Branch, B.M.A.: Clinical Meeting.

SEPT. 22.—Victorian Branch, B.M.A.: Executive Meeting.

SEPT. 23.—Queensland Branch, B.M.A.: Council Meeting.

Medical Appointments: Important Notice.

MEDICAL PRACTITIONERS are requested not to apply for any appointment mentioned below without having first communicated with the Honorary Secretary of the Branch concerned, or with the Medical Secretary of the British Medical Association, Tavistock Square, London, W.C.1.

New South Wales Branch (Honorary Secretary, 135 Macquarie Street, Sydney): Ashfield and District United Friendly Societies' Dispensary; Balmain United Friendly Societies' Dispensary; Leichhardt and Petersham United Friendly Societies' Dispensary; Manchester Unity Medical and Dispensing Institute, Oxford Street, Sydney; North Sydney Friendly Societies' Dispensary Limited; People's Prudential Assurance Company Limited; Phœnix Mutual Provident Society.

Victorian Branch (Honorary Secretary, Medical Society Hall, East Melbourne): Associated Medical Services Limited; all Institutes or Medical Dispensaries; Australian Prudential Association, Proprietary, Limited; Federated Mutual Medical Benefit Society; Mutual National Provident Club; National Provident Association; Hospital or other appointments outside Victoria.

Queensland Branch (Honorary Secretary, B.M.A. House, 225 Wickham Terrace, Brisbane, B.17): Brisbane Associated Friendly Societies' Medical Institute; Bundaberg Medical Institute. Members accepting LODGE appointments and those desiring to accept appointments to any COUNTRY HOSPITAL or position outside Australia are advised, in their own interests, to submit a copy of their Agreement to the Council before signing.

South Australian Branch (Honorary Secretary, 178 North Terrace, Adelaide): All Lodge appointments in South Australia; all Contract Practice appointments in South Australia.

Western Australian Branch (Honorary Secretary, 205 Saint George's Terrace, Perth): Wiluna Hospital; all Contract Practice appointments in Western Australia. All government appointments with the exception of those of the Department of Public Health.

Editorial Notices.

MANUSCRIPTS forwarded to the office of this journal cannot under any circumstances be returned. Original articles forwarded for publication are understood to be offered to THE MEDICAL JOURNAL OF AUSTRALIA alone, unless the contrary be stated.

All communications should be addressed to the Editor, THE MEDICAL JOURNAL OF AUSTRALIA, The Printing House, Seamer Street, Glebe, New South Wales (Telephones: MW 2651-2.)

Members and subscribers are requested to notify the Manager, THE MEDICAL JOURNAL OF AUSTRALIA, Seamer Street, Glebe, New South Wales, without delay, of any irregularity in the delivery of this journal. The management cannot accept any responsibility or recognize any claim arising out of non-receipt of journals unless such notification is received within one month.

SUBSCRIPTION RATES.—Medical students and others not receiving THE MEDICAL JOURNAL OF AUSTRALIA in virtue of membership of the Branches of the British Medical Association in the Commonwealth can become subscribers to the journal by applying to the Manager or through the usual agents and booksellers. Subscriptions can commence at the beginning of any quarter and are renewable on December 31. The rate is £3 *per annum* within Australia and the British Commonwealth of Nations, and £4 10s. *per annum* within America and foreign countries, payable in advance.